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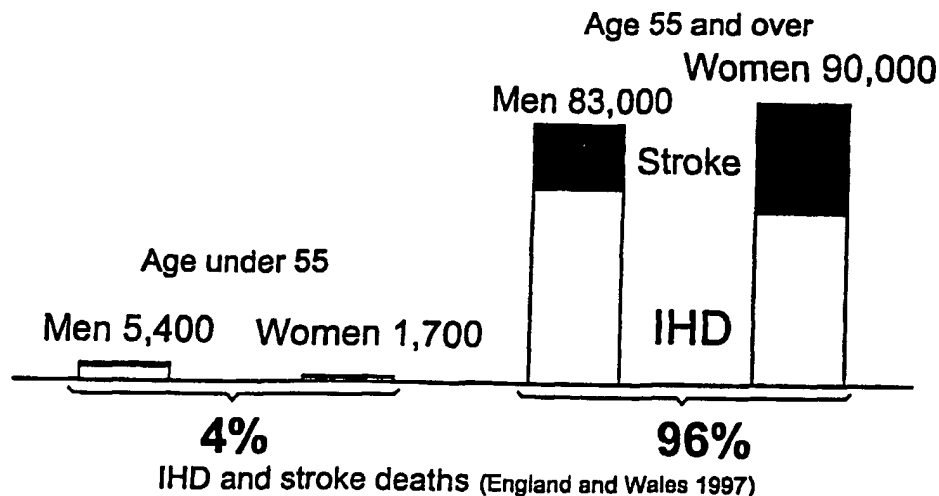
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(54) Title: **FORMULATION FOR THE PREVENTION OF CARDIOVASCULAR DISEASE**



(57) Abstract: This invention relates to a method for the prevention of cardiovascular disease, a formulation for the prevention of cardiovascular disease, the use of specified active principals for the manufacture of such a formulation for use in the method and to a method of preparing said formulation. The formulation of the present invention is a combination of active principals for use in the prevention of cardiovascular disease, notably ischaemic heart disease (including heart attacks) and stroke among the general adult population.

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Formulation for the Prevention of Cardiovascular Disease

This invention relates to a method for the prevention of cardiovascular disease, a formulation for the prevention of cardiovascular disease, the use of specified active
 5 principals for the manufacture of such a formulation for use in the method and to a method of preparing said formulation.

Cardiovascular disease, such as ischaemic heart disease (IHD) and stroke constitutes the main causes of death in most economically developed countries, accounting for about a
 10 third of all adult deaths. Table 1 shows the numbers of deaths from cardiovascular disease in England and Wales in 1998 in men and women over the age of 15, including death from heart disease and stroke and the smaller numbers of deaths from other cardiovascular causes that relate to the major cardiovascular risk factors. In total there are 200,000 deaths per year.

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Cause of death (ICD-9 code)	Men		Women	
	No of deaths	% of all deaths	No of deaths	% of all deaths
Ischaemic heart disease (410-4)	66009	25%	55024	19%
Stroke (430-8)	21432	8%	36046	13%
Heart failure (428)*, myocardial degeneration (429.1)* and hypertensive disease (401-5)	5149	2%	9172	2%
Aortic aneurysm (441)	5829	2%	3668	1%
Total	98419	38%	103914	36%

* mostly due to ischaemic heart disease

Table 1

20 The main environmental causes of these diseases, apart from cigarette smoking, are dietary and other lifestyle factors that increase the established risk factors of blood pressure, plasma or serum cholesterol (hereinafter simply referred to as serum cholesterol), plasma or serum homocysteine (hereinafter simply referred to as serum homocysteine), and impair platelet function and coagulation. Realistic changes to lifestyle factors (dietary
 25 change, weight loss, increased exercise etc.) do not generally produce sufficient change in

the cardiovascular risk factors to substantially reduce cardiovascular risk, so drug treatment to reduce the risk factors is commonly used.

The present policy for such drug treatment for reducing the incidence of cardiovascular diseases in the general population is based on intervention only when the level of one of these risk factors (especially blood pressure) is found to be particularly high (approximately the top 5% of the distribution in middle aged people and the top 10% in elderly people). Drugs have tended to be used specifically for the control of high values of each risk factor: an individual found to have what is regarded as high blood pressure but an average serum cholesterol concentration will be given treatment to lower the blood pressure but no treatment to lower the serum cholesterol. Drugs to alter platelet function (such as, for example, aspirin) and to lower serum homocysteine (such as, for example, folic acid) are rarely recommended for healthy persons. In persons who have had a non-fatal heart attack or stroke, treatment aimed at lowering blood pressure is given only if the blood pressure is at a level regarded as high (about top 10%), cholesterol lowering treatment is given if serum cholesterol is in roughly the upper half of the cholesterol distribution in the population, aspirin is routinely given, folic acid is generally not given.

The prevailing view that only extreme values of the clinical risk factors should be treated is reinforced by the commonly used terms "hypertension" (high blood pressure), "hypercholesterolaemia" (high serum cholesterol), "hyperhomocysteinaemia" (high serum homocysteine) implying that it is the increase from the normal value which is the damaging or dangerous condition. "Normal", as used herein, means having a level of risk factor (such as blood pressure, serum cholesterol, serum homocysteine) which is around the population average and therefore not judged to be high on the basis of conventional clinical practice or published professional guidelines (such as described, for example, in WO-A-97/38694 in the name of Merck & Co., Inc). "High" values have been defined in published professional guidelines as above a specified absolute value which is often close to the 90th or 95th centile of the risk factor in the population.

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Under current clinical practice therefore, individuals found to have high values of the risk factors of cardiovascular disease are treated to reduce the risk factors (e.g. blood pressure or lipid level) to the so-called normal value, but no lower, by the application of one of

many active principals known in the art. These high values may come to light as a result of routine health screening or as a result of an individual undergoing tests for a related or unrelated condition. Alternatively an individual who has had the misfortune of suffering from a cardiovascular insult such as a heart attack or stroke, may receive treatment for one
5 or more of the risk factors associated with cardiovascular disease.

The proposition underlying this invention is that this policy and the practical clinical management of the policy is inefficient. There is, in fact, a considerable prejudice in the art which focuses clinical attention on the control of what are considered to be abnormally
10 high risk factors once an individual presents with one or more high risk factors.

The present invention is based, in part, on the realisation of the following:

(1) Whilst cardiovascular disease is responsible for 37% of all deaths in England and
15 Wales, treating individuals in the top 5% or so of a single risk factor distribution cannot make a significant impact on a group of diseases common enough to cause 37% of all deaths, even if the treatment were totally successful.

(2) Despite the aetiological importance of the cardiovascular risk factors, their
20 effectiveness as screening tests in predicting risk in an individual is relatively weak (reference 10). Only about 20% of all deaths from heart disease and stroke occur in persons whose values of any of the risk factors lie in the top 10% of the distribution among persons in any specified age group. Since most cases of cardiovascular disease, such as myocardial infarction, occur in persons with risk factors close to the population average,
25 seeking to identify persons who will have a heart attack or stroke by identifying only persons with especially high values of risk factors necessarily has a limited impact. Importantly, the average values of serum cholesterol, blood pressure and serum homocysteine in Britain and other Western populations where heart disease and stroke are common are high compared with the values in populations in which heart disease and
30 stroke are rare. Also the distribution of values around this "high" average is relatively narrow. Figures 7 to 9 show the relative distributions of blood pressure and serum cholesterol in persons who subsequently die from a stroke or ischaemic heart disease, and the relative distributions of blood pressure and serum cholesterol in persons of the same

age who do not subsequently die from these diseases. There is substantial overlap in the distributions indicating that the relevant risk factors (blood pressure or serum cholesterol) are poor discriminators of those who will and those who will not be affected. For example, if a serum cholesterol cut off level was selected that identified the 5% of people with highest serum cholesterol levels who did not die of ischaemic heart disease over the period of follow-up (false positive rate, FPR = 5%), only 15% of persons who did die of ischaemic heart disease over the same period of follow-up would be correctly identified (detection rate DR, = 15%). Thus, 85% of future deaths from ischaemic heart disease would be missed. The false positive rate (FPR) refers to the proportion of persons not developing the specified disease (stroke or ischaemic heart disease) whose value of the risk factor exceeds the specified value. The detection rate (DR) refers to the proportion of persons who do develop the disease whose values of the risk factor exceeds the specified value.

(3) Offering treatment to reduce the risk of a heart attack or stroke by reducing any one of these risk factors in isolation has a limited impact on the potential for reducing risk. Heart disease and stroke are common in Western countries because the average values of all the important risk factors are high and their effects, being independent of each other, interact in a multiplicative (or synergistic) manner. A combined treatment regimen aimed at changing several risk factors together is necessary to achieve a substantial reduction in risk.

(4) Present clinical practice fails to take account of the fact that the increased risk of cardiovascular disease with a particularly high level of one of the known risk factors represents merely that part of a dose response relationship lying above a population-determined normal level. The present inventors have demonstrated and discuss herein, that reducing the level of a risk factor below the accepted normal value gives rise to a concomitant reduction in the risk of cardiovascular disease. This finding and proof demonstrates that treatment by treating abnormally high levels of a risk factor is not efficient because there is no risk threshold. Even within the population "normal" range, further reduction of the risk factor continues to provide further reduction in the risk of cardiovascular disease. By detailed analysis of the literature and the application of techniques of biomedical statistics and meta-analysis, the present inventors have shown

that there is no effective lower threshold of the risk of cardiovascular disease in relation to the level of a particular risk factor in economically developed populations, below which there is no further reduction in risk for further reductions in the risk factor.

- 5 For example, Figure 1 is a logarithmic plot of the relative risk of suffering a stroke against the diastolic blood pressure. The advantage of using a log scale is that, if there is a strong link between the risk factor and the disease, there is a constant proportional reduction for a given unit change in the risk factor from any point on its distribution. The average diastolic blood pressure in the population is in the region of 85mmHg (see Figures 7 and 8)
- 10 and it can readily be seen that an individual exhibiting a higher blood pressure has an increased risk of suffering from a stroke. However, what is also apparent is that reducing the blood pressure, below that considered to be normal, by the same token reduces the risk at a similar rate on this logarithmic scale. Reductions in blood pressure among people with blood pressure which is not regarded as high, using blood pressure reducing agents in
- 15 appropriate dosages, do not, or only very rarely, cause serious side effects, but do reduce the risk of cardiovascular disease. Significantly, the evidence is that the risk continues to be reduced across the whole range of blood pressure values found in the population and does not reach a threshold of risk at or around the average level in the population. Although as currently understood, the risk of cardiovascular disease increases when one of
- 20 the risk factors exceeds the population average value, the risk does not remain constant below this value, but decreases with further decrease of the risk factor below the normal value. This is shown herein in Figures 1 to 5.

- It can thus be seen that there are considerable advantages in reducing the level of risk
- 25 factors such as blood pressure, serum lipid levels, platelet function levels and serum homocysteine levels below the normal levels exhibited in a given population, even where none of these levels exceeds the normal level in an individual. Any reduction in one or more of the risk factors of blood pressure, serum lipid levels, platelet function levels and serum homocysteine levels provides a significant reduction in the risk of cardiovascular
- 30 disease, even if the levels in a particular individual are not high.

Effecting a reduction in the risk factor in individuals with a normal level of the risk factor is contrary to clinical practice, thus this proposal runs entirely contrary to the art.

The basis of the present invention is therefore that individuals should be treated irrespective of whether they exhibit particularly high values of any of the risk factors associated with cardiovascular disease or have a clinical history of cardiovascular disease, and that all risk factors should be changed. This is a considerable departure from the normal clinical practice and dogma.

The object of the present invention is to provide a method and formulations to address a significant clinical problem in the prior art. Current medical practice concentrates on the treatment of individuals who exhibit high levels of cardiovascular risk factors, such as high blood pressure, high serum lipid levels and high serum homocysteine levels, by treating these abnormal factors with various pharmaceuticals. The present invention demonstrates that this practice is inefficient since an extremely high proportion of the population is at risk of developing, and dying from cardiovascular disease with normal levels of or without knowing even if levels are above normal. By proposing reducing these levels in all patients, a significant improvement in the general health of the world's population can be achieved.

Combination drug therapies for the treatment of the risk factors of cardiovascular disease are known. The individual active principals used to treat the risk factors independently are well known and are, on occasion, used in combination. For example, in the treatment of high blood pressure, if an individual appears to fail to respond to a particular class of blood pressure reducing active principal, the dose of that drug will be increased to a higher dose, but if that still fails to give rise to the required blood pressure reduction, a second blood pressure lowering active principal may be administered in combination. In this clinical scenario, of course, the availability of a single formulation containing two blood pressure reducing active principals may not be useful as the whole clinical procedure requires careful dose adjustment in response to the condition of the patient. Recently, clinical practice has been to commence treatment of persons with abnormally high blood pressure with two different blood pressure lowering drugs in combination in some cases.

It has also been proposed to administer active principals against different risk factors in a single formulation. In WO-A-97/38694 (Merck & Co., Inc) for example, a lipid reducing

drug, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (HMG-CoA RI - a statin), is formulated together with folic acid (a homocysteine reducing drug) to make a combined formulation which is said to be more convenient for patient compliance as it is reasonably easy to add the small amount of folic acid necessary to an existing daily HMG-CoA RI unit dosage form. WO-A-97/38694 neither demonstrates nor suggests any additional physiological benefit of the combination. WO-A-97/38694 suggests very generally that other active agents may be added, listing a large and varied range of active agents with no specificity or indication of their intended purpose. Most significantly, there is no indication whatsoever of administering a combined formulation to individuals without measuring, or if measured regardless of the level, of any of the risk factors associated with cardiovascular disease. WO-A-98/11896 (Merck & Co., Inc) parallels this disclosure proposing a combination of an HMG-CoA RI with a platelet aggregation inhibitor. Neither the rationale for the combination nor any indication of advantage is disclosed. WO-A-98/19690 (Bristol-Myers Squibb Company) discloses combinations of folic acid (with or without vitamin B12) together with an agent selected to dilate the brain vasculature, this agent in some selections being a drug that is also in use as a blood pressure reducing agent. There are however critical distinctions from the present invention. The drugs are selected as vasodilating agents, not because they lower blood pressure. The folic acid is used only in persons with early Alzheimer's disease, not the general population and only in such persons with high homocysteine, not all such persons. The combination is not specified as a single preparation formulation. Spaulding *et al* Circulation (1998), 98(8), (757-765) describe clinical trials on the administration of aspirin and various ACE inhibitors to patients with ischaemic heart disease that is causing chronic heart failure. There are again critical distinctions from the present invention. The ACE inhibitor is used to control heart failure, not to prevent recurrent myocardial infarction or other recurrent ischaemic events; there is therefore no disclosure to synergy with the aspirin. The combination is to be used only in patients with heart failure, not in the general population. The combination is not specified as a single preparation formulation. Forbes *et al* Semin. Thromb. Hemostasis (1999), 25 Suppl., 55-59 describe combinations of one or other of two separate types of blood pressure reducing agents with a platelet aggregation inhibitor in trials on patients already exhibiting peripheral arterial obstructive disease or coronary artery disease. The trial concluded that the coadministration of the platelet aggregation agent did not interfere with the control of hypertension or angina. Again there

are critical distinctions from the present invention. The calcium channel blocker was to be used to lower blood pressure only in patients selected as having particularly high blood pressure (hypertension), and the beta-blocker was to be used either to treat hypertension in the same way or to treat angina (that is to reduce the frequency of the pain). The combination is to be used only in persons with peripheral or coronary arterial disease, not the general population. The combination is not specified as a single preparation formulation.

According to the present invention there is provided a method for reducing the risk of cardiovascular disease comprising administering simultaneously, separately or sequentially, active principals from at least two of the following three categories:

- i) at least one blood pressure lowering agent,
 - ii) at least one lipid-regulating agent, and
 - iii) at least one serum homocysteine lowering agent,
- with or without at least one platelet function altering agent, to an individual without measuring, or if measured regardless of the level of, one or more of the risk factors of cardiovascular disease selected from blood pressure, serum cholesterol, serum homocysteine or platelet function.

Alternatively, there is provided a method for reducing the risk of cardiovascular disease comprising administering simultaneously, separately or sequentially, at least one blood pressure lowering agent and at least one active principal from at least one of the following two categories:

- i) at least one lipid-regulating agent, and
 - ii) at least one serum homocysteine lowering agent,
- with or without at least one platelet function altering agent, to an individual without measuring, or if measured regardless of the level of, one or more of the risk factors of cardiovascular disease selected from blood pressure, serum cholesterol, serum homocysteine or platelet function.

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As used herein, the term "cardiovascular disease" means any atheromatous arterial disease, any non-syphilitic arterial aneurysm, and cerebral and subarachnoid haemorrhage. The cardiovascular system encompasses the entire vascular system of the body including the

heart itself. Thus the term "cardiovascular disease" includes, but is not limited to, ischaemic heart disease (IHD), angina pectoris, coronary heart disease, stroke, transient ischaemic attacks, cerebrovascular disease, hypertensive disease, aortic aneurysm, peripheral arterial disease and retinal arterial disease.

5

The physiological effects of blood pressure lowering agents, lipid-regulating agents, platelet function altering agents and serum homocysteine lowering agents in reducing the risk of cardiovascular disease have been found to be independent of each other. The recognition of the combined effect of using these four different categories of drugs together is novel. At the preferred dosages of these drugs, the prevalence of the ratio of benefit to hazard, i.e. the ratio of the reduction in the incidence of cardiovascular disease to the prevalence of adverse effects of the drugs, is high. The estimation of the preventive effect of the formulation of the present invention and its application in a preventive setting is novel. In fact, a policy of treating a person in the general population, selected only on the basis of his or her age and sex, preventively against cardiovascular disease is contrary to the present policy for reducing the incidence of cardiovascular disease, which is based on intervention only if one or more risk factors are found to be high.

It is of considerable significance to the present invention that the method is applied to an individual without measuring, or if measured regardless of the level of, one or more of the risk factors of cardiovascular disease. As discussed above, only 5-10% of the population exhibit values of any of the risk factors of cardiovascular disease sufficiently high to warrant drug treatment under present clinical practice, but 37% of the population die from a cardiovascular disease. The effort involved in dealing with those individuals who have particularly high values of risk factors, in terms of medical analysis, clinician's time, the development of treatment programmes etc far outweighs the simple solution proposed here of reducing the risk factors in all persons above a specified age.

The correlation between age and the risk of cardiovascular disease is very strong as demonstrated in Figure 6 herein. It is stronger than the relationship with risk factors of blood pressure, serum cholesterol and serum homocysteine. The data shown in Figure 6 demonstrate that it is possible to determine a cut off age for routine treatment which may

be independent of the need for every individual to undergo time consuming and costly tests.

Preferably, the method is applied to an individual above a predetermined age, for example
5 an individual who may have no clinical symptoms of cardiovascular disease, the only
criterion being that he or she is above a predetermined age. The predetermined age will
vary from population to population according to the incidence of cardiovascular disease or
according to the age distribution of cases (which depends on patterns of diet, smoking and
other factors). The predetermined age can be determined simply by determining the age
10 above which 95% of the deaths from ischaemic heart disease or stroke occur. Typically
the predetermined age is from 45 to 65. The age by which 5% of all deaths from heart
disease and stroke have occurred in England and Wales is about 55 for men and about 65
for women. Thus, most preferably, the method is applied to an individual above the age of
55 for males and above the age of 65 for females, based on England and Wales mortality
15 data, and in other European countries the predetermined age would be similar.
Alternatively, for simplicity, a single age preferably from 45 to 65, for example about 55,
may be used for both men and women.

Alternatively, the method may be used when an individual's annual risk of ischaemic heart
20 disease and stroke, calculated from their age, sex and measurable risk factors including
blood pressure, serum cholesterol, serum homocysteine and smoking history, exceeds a
predetermined value (such as for example 2% per year). The predetermined age may be
determined using known statistical analyses based on data obtained from the population in
which the individual resides. Preferably, the method is applied to individuals in the
25 population above the age for the gender above which 95% of the deaths due to ischaemic
heart disease or stroke occur.

The method may also be applied to an individual who has previously been diagnosed as
having had the clinical symptoms of cardiovascular disease, irrespective of age.
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Although the active principals may be administered simultaneously, separately or
sequentially, preferably the active principals are administered simultaneously in a single
dosage form. This is a major departure from present clinical practice. Present practice is

to offer treatment (with the exception of aspirin) if the value of a particular risk factor is particularly high, and then to treat the risk factor that is high (even though risk of disease may be high and this would respond to the lowering of all risk factors).

- 5 For all of the active principals, the dosage is selected to maximise the reduction of risk of cardiovascular disease whilst minimising undesirable side effects. The dose will depend on the active principal concerned. The preferred doses are calculated to be at levels optimising the ratio of benefit to hazard, i.e. the ratio of reduction of the risk of cardiovascular disease to the risk of adverse effects of the administered agent. This
- 10 optimisation is well within the scope of the skilled person with the benefit of appropriate experimental trials. The most preferred doses for lipid-regulating agents are within the therapeutic range recommended by the British National Formulary of March 2000 (see Table 2). The most preferred doses for platelet function altering agents are at the lower end of the therapeutic range recommended by the British National Formulary of March
- 15 2000 (see Table 2) (for example about 75 mg/day of aspirin). The most preferred doses for blood pressure lowering agents are half of the doses at the lower end of the therapeutic range recommended in the British National Formulary of March 2000 (see Table 2). The most preferred dose of folic acid is about 0.8 mg/day.

BNF Section	Active Principal	BNF Recommended Dose	Most Preferred Daily Dose
2.2.1 Thiazide-like diuretics	bendroflume- thiazide/ bendrofluazide	hypertension, 2.5mg in the morning, higher doses rarely necessary	about 1.25mg
	chlorthalidone	hypertension, 25mg in the morning, increased to 50mg if necessary	about 12.5mg
	cyclopenthia- zide	hypertension, initially 250µg daily in the morning, increased if necessary to 500µg daily	about 125µg
	hydrochloro- thiazide	hypertension, 25mg daily, increased to 50mg daily if necessary; in some patients (especially the elderly) an initial dose of 12.5mg daily may be sufficient	about 12.5mg
	indapamide	2.5mg in the morning	about 1.25mg
	mefruside	initially 25-50mg in the morning, maintenance 25mg daily or on alternate days	about 12.5mg

	metolazone	hypertension, initially 5mg in the morning, maintenance 5mg on alternate days	about 2.5mg on alternate days
	polythiazide	usually 1-4mg daily, in hypertension 500µg daily may be adequate	about 1mg
	xipamide	hypertension, 20mg in the morning	about 10mg
2.4 Beta blockers	propranolol hydrochloride	by mouth, hypertension, initially 80mg twice daily, increased at weekly intervals as required, maintenance 160-320mg daily	about 80mg
	acebutolol	hypertension, initially 400mg once daily or 200mg twice daily, increased after 2 weeks to 400mg twice daily if necessary	about 200mg
	atenolol	by mouth, hypertension, 50mg daily (higher doses rarely necessary)	about 25mg
	betaxolol hydrochloride	20mg daily (elderly patients 10mg), increased to 40mg if required	about 10mg
	bisoprolol fumarate	usual dose 10mg daily (5mg may be adequate in some patients), max. recommended dose 20mg daily	about 5mg
	carvedilol	hypertension, initially 12.5mg once daily, increased after 2 days to usual dose of 25mg once daily, if necessary may be further increased at intervals of at least 2 weeks to max. 50mg daily in single or divided doses; elderly initial dose of 12.5mg daily may provide satisfactory control	about 12.5mg
	celiprolol hydrochloride	200mg once daily in the morning, increased to 400mg once daily if necessary	about 100mg
	labetalol hydrochloride	by mouth, initially 100mg (50mg in elderly) twice daily with food, increased at intervals of 14 days to usual dose of 200mg twice daily, up to 800mg daily in 2 divided doses (3-4 divided doses if higher), max. 2.4g daily	about 200mg
	metoprolol tartrate	by mouth, hypertension, initially 100mg daily, maintenance 100-200mg daily in 1-2 doses	about 50mg
	nadolol	hypertension, 80mg daily, increased at weekly intervals if required, max. 240mg daily	about 40mg
	nebivolol	5mg daily; elderly initially 2.5mg daily, increased if necessary to 5mg daily	about 2.5mg

	oxprenolol hydrochloride	hypertension, 80-160mg daily in 2-3 divided doses, increased as required, max. 320mg daily	about 40mg
	pindolol	hypertension, initially 5mg 2-3 times daily or 15mg once daily, increased as required at weekly intervals, usual maintenance 15-30mg daily, max. 45mg daily	about 7.5mg daily
	timolol maleate	hypertension, initially 5mg twice daily or 10mg once daily, gradually increased if necessary to max. 60mg daily (given in divided doses above 20mg daily)	about 5mg
2.5.1 Vasodilator antihyper- tensive drugs	hydralazine hydrochloride	by mouth, hypertension, 25mg twice daily, increased to usual max. 50mg twice daily	about 25mg daily
	minoxidil	initially 5mg (elderly 2.5mg) daily in 1-2 doses, increased by 5-10mg every 3 or more days, max. usually 50mg daily	about 12.5mg
2.5.5.1 ACE inhibitors	captopril	hypertension, used alone initially 12.5mg twice daily; if used in addition to diuretic or in elderly initially 6.25mg twice daily (first dose at bedtime); usual maintenance dose 25mg twice daily; max. 50mg twice daily (rarely three times daily in severe hypertension)	about 25mg daily
	cilazapril	hypertension, initially 1-1.25mg once daily (initial dose reduced in those receiving a diuretic, in the elderly, in renal impairment and in severe hepatic impairment - consult product literature), usual maintenance dose 2.5-5mg daily, max. 5mg daily renovascular hypertension, initially 250-500µg once daily, then adjusted according to response	about 1.25mg
	enalapril maleate	hypertension, used alone, initially 5mg once daily; if used in addition to diuretic, in elderly patients or in renal impairment initially 2.5mg daily; usual maintenance dose 10-20mg once daily; in severe hypertension may be increased to max. 40mg daily	about 5mg
	fosinopril	hypertension, initially 10mg daily, increased if necessary after 4 weeks, usual dose range 10-40mg (doses over 40mg not shown to increase efficacy)	about 5mg

	imidapril hydrochloride	initially 5mg daily before food; if used in addition to diuretic, in elderly, in patients with heart failure, angina or cerebrovascular disease, or in renal or hepatic impairment, initially 2.5mg daily; if necessary increase dose at intervals of at least 3 weeks; usual maintenance dose 10mg once daily; max. 20mg daily (elderly 10mg daily)	about 5mg
	lisinopril	hypertension, initially 2.5mg daily; usual maintenance dose 10-20mg daily; max. 40mg daily	about 5mg
	moexipril hydrochloride	used alone, initially 7.5mg once daily; if used in addition to diuretic, with nifedipine, in elderly, in renal or hepatic impairment, initially 3.75mg once daily; usual range 15-30mg once daily; doses above 30mg daily not shown to increase efficacy	about 7.5mg
	perindopril	hypertension, initially 2mg daily (before food), usual maintenance dose 4mg once daily, max. 8mg daily	about 2mg
	quinapril	hypertension, initially 10mg once daily; with a diuretic, in elderly, or in renal impairment initially 2.5mg daily; usual maintenance dose 20-40mg daily in single or 2 divided doses; up to 80mg daily has been given	about 10mg
	ramipril	hypertension, initially 1.25mg daily, increased at intervals of 1-2 weeks, usual range 2.5-5mg once daily, max. 10mg daily	about 1.25mg
	trandolapril	hypertension, initially 500µg once daily, increased at intervals of 2-4 weeks, usual range 1-2mg once daily, max. 4mg daily	about 0.5mg
2.5.5.2 Angiotensin II receptor antagonists	candesartan cilexetil	initially 4mg (2mg in hepatic and renal impairment) once daily adjusted according to response, usual maintenance dose 8mg once daily, max. 16mg once daily	about 4mg
	irbesartan	150mg once daily, increased if necessary to 300mg once daily (in haemodialysis or in elderly over 75 years, initial dose of 75mg once daily may be used)	about 75mg

	losartan potassium	usually 50mg once daily (elderly over 75 years, moderate to severe renal impairment, intravascular volume depletion, initially 25mg once daily), if necessary increased after several weeks to 100mg once daily	about 25mg
	telmisartan	40mg once daily, increased if necessary to 80mg once daily	about 20mg
	valsartan	usually 80mg once daily (elderly over 75 years, mild to moderate hepatic impairment, moderate to severe renal impairment, intravascular volume depletion, initially 40mg once daily), if necessary increased after at least 4 weeks to 160mg daily (80mg daily in hepatic impairment)	about 40mg
2.6.2 Calcium channel blockers	amlodipine besilate	hypertension, initially 5mg once daily, max. 10mg once daily	about 2.5mg
	diltiazem hydrochloride	see individual preparations	
	felodipine	hypertension, initially 5mg (elderly 2.5mg) daily in the morning, usual maintenance 5-10mg once daily, doses above 20mg daily rarely needed	about 2.5mg
	isradipine	2.5mg twice daily (1.25mg twice daily in elderly, hepatic or renal impairment), increased if necessary after 3-4 week to 5mg twice daily (exceptionally up to 10mg twice daily), maintenance 2.5 or 5mg once daily may be sufficient	about 2.5mg daily
	lacidipine	initially 2mg as a single daily dose, preferably in the morning; increased after 3-4 weeks to 4mg daily, then if necessary to 6mg daily	about 2mg
	lercanidipine hydrochloride	initially 10mg once daily; increased if necessary after at least 2 weeks to 20mg daily	about 5mg
	nicardipine hydrochloride	initially 20mg 3 times daily, increased after at least 3 days to 30mg 3 times daily (usual range 60-120mg daily)	about 30mg daily
	nifedipine	see individual preparations	
	nisoldipine	initially 10mg daily, preferably before breakfast; if necessary increase at intervals of at least 1 week; max. 40mg daily	about 5mg

2.9 Platelet function altering drugs	aspirin	75-300mg daily	about 75mg
	clopidogrel	75mg once daily	about 75mg
	dipyridamole	by mouth: 300-600mg daily in 3-4 divided doses before food modified-release preparations, see individual preparations by intravenous injection: diagnostic only, consult product literature	about 300mg
	ticlopidine hydrochloride	250mg twice daily	about 500mg daily
2.12 Lipid-regulating drugs	colestyramine	lipid reduction (after initial introduction over 3-4 weeks) 12-24g daily in water (or other suitable liquid) in single or up to 4 divided doses, up to 36g daily if necessary child 6-12 years see product literature	about 12g
	colestipol hydrochloride	5g 1-2 times daily in liquid, increased if necessary at intervals of 1-2 months to max. of 30g daily (in single or 2 divided doses)	about 5g
	bezafibrate	see individual preparations	
	ciprofibrate	100mg daily	about 100mg
	clofibrate	over 65kg, 2g daily (50-65kg, 1.5g daily) in 2 or 3 divided doses	about 2g
	fenofibrate	see individual preparations	
	gemfibrozil	1.2g daily, usually in 2 divided doses; range 0.9-1.5g daily	about 1.2g
	atorvastatin	primary hypercholesterolaemia and combined hyperlipidaemia, usually 10mg once daily familial hypercholesterolaemia, initially 10mg daily, increased at intervals of 4 weeks to 40mg once daily; if necessary further increased to max. 80mg once daily (or combined with anion-exchange resin in heterozygous familial hypercholesterolaemia)	about 10mg
	cerivastatin sodium	initially 100µg once daily in the evening, increased by increments of 100µg at intervals of not less than 4 weeks to max. 300µg once daily (200µg daily in moderate to severe renal impairment)	about 200µg

	fluvastatin	initially 20-40mg daily in the evening; usual range 20-40mg daily in the evening, adjusted at intervals of 4 weeks; up to 40mg twice daily may be required	about 20mg
	pravastatin sodium	usual range 10-40mg once daily at night, adjusted at intervals of not less than 4 weeks	about 20mg
	simvastatin	hyperlipidaemia, 10mg daily at night, adjusted at intervals of not less than 4 weeks; usual range 10-40mg once daily at night coronary heart disease, initially 20mg once daily at night	about 20mg

Table 2

- For drugs used to lower blood pressure, the dose of an active principal is below the lower therapeutic dosage for the indication of the active principal. As used herein, the term “therapeutic dosage” is intended to refer to the commonly used dose in clinical practice for the treatment of high levels of the risk factor or for the treatment of cardiovascular disease by the separate active principal. The most preferred doses for blood pressure lowering agents are half of the doses at the lower end of the therapeutic range recommended in the British National Formulary of March 2000. This is in order to maximise the therapeutic benefit of the combination of agents, while minimising the risks of adverse effects of the individual agents. An analysis of randomised placebo controlled trials of the individual drugs (given in the references) shows that with half the present recommended dose the reduction in blood pressure is only 20% lower than with the full recommended dose, while the reduction in adverse effects is much greater. Most preferably, the dose of a blood pressure lowering agent is about half the recommended dose (or, where a range of doses is given, half of the recommended dose at the lower end of the recommended therapeutic range) for the blood pressure lowering agent.
- Preferably the blood pressure lowering agent is a diuretic, a beta blocker, an ACE inhibitor, an angiotension-II receptor antagonist, a vasodilator antihypertensive drug, and/or a calcium-channel blocker. More preferably the blood pressure lowering agent is a diuretic, and/or a beta blocker, and/or an ACE inhibitor.

Preferably the diuretic is a thiazide or thiazide-like diuretic. Preferably the thiazide or thiazide-like diuretic is hydrochlorothiazide, chlorthalidone, indapamide, bendroflumethiazide, chlorothiazide, metolazone, cyclopenthiazide, polythiazide, mefruside, or xipamide. Most preferably the thiazide or thiazide-like diuretic is hydrochlorothiazide. Thiazide or thiazide-like diuretics are categorised in Section 2.2.1 of the British National Formulary of March 2000 and other equivalent national formularies or pharmacopoeias, such as for example the "Physicians Desk Reference" (PDR) and "Martindale: The Extra Pharmacopoeia" (Reynolds JEF (ed.), London, Royal Pharmaceutical Society, 1996). Preferably the hydrochlorothiazide is administered in an amount of from about 2.5 mg to about 62.5 mg per day; more preferably the hydrochlorothiazide is administered in an amount of from about 5 mg to about 37.5 mg per day; most preferably the hydrochlorothiazide is administered in an amount of about 12.5 mg per day.

Preferably the beta blocker is a β_1 -selective adrenoceptor antagonist; preferably the β_1 selective adrenoceptor antagonist is atenolol, bisoprolol, betaxolol, metoprolol, celiprolol, or acebutolol. Alternatively the beta blocker is a non-selective beta-adrenoceptor antagonist; preferably the non-selective beta-adrenoceptor antagonist is pindolol, propranolol, oxprenolol, sotalol, timolol, or nadolol. Alternatively the beta blocker is a drug with combined β - and α -adrenoceptor blocking action; preferably this drug is carvedilol, or labetalol. Most preferably the beta blocker is atenolol. Beta blockers are categorised in Section 2.4 of the British National Formulary of March 2000 and in other equivalent national formularies or pharmacopoeias. Preferably the atenolol is administered in an amount of from about 5 mg to about 125 mg per day; more preferably the atenolol is administered in an amount of from about 10 mg to about 75 mg per day; most preferably the atenolol is administered in an amount of about 25 mg per day.

Preferably the ACE inhibitor is enalapril, perindopril, captopril, cilazapril, trandolapril, fosinopril, quinapril, lisinopril, ramipril, or moexipril. Most preferably the ACE inhibitor is enalapril. ACE inhibitors are categorised in Section 2.5.5.1 of the British National Formulary of March 2000 and in other equivalent national formularies or pharmacopoeias. Preferably the enalapril is administered in an amount of from about 1 mg to about 25 mg per day; more preferably the enalapril is administered in an amount of from about 1.5 mg

to about 15 mg per day; most preferably the enalapril is administered in an amount of about 5 mg per day.

Preferably the angiotension-II receptor antagonist is losartan, valsartan, candesartan,
5 eprosartan, irbesartan or telmisartan. More preferably the angiotension-II receptor
antagonist is losartan. Angiotension-II receptor antagonists are categorised in Section
2.5.5.2 of the British National Formulary of March 2000 and in other equivalent national
formularies or pharmacopoeias. Preferably the losartan is administered in an amount of
10 amount of from about 10 mg to about 75 mg per day; most preferably the losartan is
administered in an amount of about 25 mg per day.

Preferably the vasodilator antihypertensive drug is hydralazine. Vasodilator
antihypertensive drugs are categorised in Section 2.5.1 of the British National Formulary
15 of March 2000 and in other equivalent national formularies or pharmacopoeias. Preferably
the hydralazine is administered in an amount of from about 2.5 mg to about 62.5 mg per
day; more preferably the hydralazine is administered in an amount of from about 5 mg to
about 37.5 mg per day; most preferably the hydralazine is administered in an amount of
about 12.5 mg per day.

20

Preferably the calcium-channel blocker is amlodipine, diltiazem, felodipine, isradipine,
lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine or nisoldipine. More
preferably the calcium-channel blocker is amlodipine. Calcium-channel blockers are
categorised in Section 2.6.2 of the British National Formulary of March 2000 and in other
25 equivalent national formularies or pharmacopoeias. Preferably the amlodipine is
administered in an amount of from about 0.5 mg to about 12.5 mg per day; more preferably
the amlodipine is administered in an amount of from about 0.8 mg to about 7.5 mg per day;
most preferably the amlodipine is administered in an amount of about 2.5 mg per day.
Preferably the amlodipine is administered as the maleate or besilate.

30

Preferably the formulation of the present invention comprises more than one blood
pressure lowering agent. More preferably the formulation comprises two blood pressure
lowering agents. Most preferably the formulation comprises three blood pressure lowering

agents. Preferably the blood pressure lowering agents will be independently selected from a diuretic, a beta blocker, an ACE inhibitor, an angiotensin II receptor antagonist, and a calcium channel blocker. More preferably the blood pressure lowering agents will be independently selected from a diuretic, a beta blocker, and an ACE inhibitor.

5

- Preferably the lipid-regulating agent is a 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitor, also called a statin. Preferably the statin is atorvastatin, simvastatin, cerivastatin, fluvastatin, or pravastatin. More preferably the statin is atorvastatin or simvastatin. Most preferably the statin is atorvastatin. Lipid-regulating
- 10 drugs are categorised in Section 2.12 of the British National Formulary of March 2000 and in other equivalent national formularies or pharmacopoeias. Preferably the atorvastatin is administered in an amount of from about 2 mg to about 50 mg per day; more preferably the atorvastatin is administered in an amount of from about 3 mg to about 30 mg per day; most preferably the atorvastatin is administered in an amount of about 10 mg per day.
- 15 Preferably the simvastatin is administered in an amount of from about 2 mg to about 60 mg per day; more preferably the atorvastatin is administered in an amount of from about 3 mg to about 40 mg per day; most preferably the atorvastatin is administered in an amount of from about 10 mg to about 20 mg per day.
- 20 Preferably the platelet function altering agent is aspirin, ticlopidine, dipyridamole, clopidogrel, or a glycoprotein IIb/IIIa receptor inhibitor such as abciximab, or a non-steroidal anti-inflammatory drug such as ibuprofen. Most preferably the platelet function altering agent is aspirin. Platelet function altering agents are categorised in Section 2.9 of the British National Formulary of March 2000 and in other equivalent national formularies
- 25 or pharmacopoeias. Non-steroidal anti-inflammatory drugs are categorised in Section 10.1.1 of the British National Formulary of March 2000 and in other equivalent national formularies or pharmacopoeias. Preferably the aspirin is administered in an amount of from about 15 mg to about 500 mg per day; more preferably the aspirin is administered in an amount of from about 25 mg to about 250 mg per day; most preferably the aspirin is
- 30 administered in an amount of about 75 mg per day.

Preferably the serum homocysteine lowering agent is folic acid, vitamin B6, or vitamin B12, or a combination of two or three of these. Most preferably the serum homocysteine

lowering agent is folic acid. Preferably the folic acid is administered in an amount of from about 0.2 mg to about 4 mg per day; more preferably the folic acid is administered in an amount of from about 0.4 mg to about 2 mg per day; most preferably the folic acid is administered in an amount of about 0.8 mg per day.

5

Most preferably the formulation used in the method of the invention comprises:

- i) about 12.5 mg hydrochlorothiazide, about 25 mg atenolol, and about 5 mg enalapril as blood pressure lowering agents,
- ii) about 10 mg atorvastatin as lipid-regulating agent,
- 10 iii) about 75 mg aspirin as platelet function altering agent, and
- iv) about 0.8 mg folic acid as serum homocysteine lowering agent.

Alternatively the formulation used in the method of the invention comprises:

- i) about 12.5 mg hydrochlorothiazide, about 25 mg atenolol, and about 5 mg enalapril as blood pressure lowering agents,
- 15 ii) about 10-20 mg simvastatin as lipid-regulating agent,
- iii) about 75 mg aspirin as platelet function altering agent, and
- iv) about 0.8 mg folic acid as serum homocysteine lowering agent.

20 Alternatively the formulation used in the method of the invention comprises:

- i) about 12.5 mg hydrochlorothiazide, about 25 mg atenolol, and about 2.5mg amlodipine maleate as blood pressure lowering agents,
- ii) about 10-20 mg simvastatin as lipid-regulating agent,
- iii) about 75 mg aspirin as platelet function altering agent, and
- 25 iv) about 0.8 mg folic acid as serum homocysteine lowering agent.

Alternatively the formulation used in the method of the invention comprises:

- i) about 12.5 mg hydrochlorothiazide, about 2.5mg amlodipine maleate, and about 5 mg enalapril as blood pressure lowering agents,
- 30 ii) about 10-20 mg simvastatin as lipid-regulating agent,
- iii) about 75 mg aspirin as platelet function altering agent, and
- iv) about 0.8 mg folic acid as serum homocysteine lowering agent.

Optionally the method of the present invention further comprises an active principal from a fifth category comprising anti-oxidants. Preferably the antioxidant is vitamin E.

Preferably the active principals are administered orally to a patient.

5

The use of the formulation may reduce the risk of cardiovascular disease by at least 80%. Preferably, the use of the formulation reduces the risk of cardiovascular disease by at least 50%, more preferably the use of the formulation reduces the risk of cardiovascular disease by at least 60%, even more preferably the use of the formulation reduces the risk of
10 cardiovascular disease by at least 70%, most preferably the use of the formulation reduces the risk of cardiovascular disease by at least 80%.

The invention further provides formulations for use in the treatment of cardiovascular disease.

15

In a further aspect of the invention there is provided a formulation comprising at least two blood pressure lowering agents, each selected from a different physiological mode of action selected from a diuretic, a beta blocker, an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, and a calcium channel blocker, and an
20 active principal from at least two of the following three categories:

- i) at least one lipid-regulating agent,
- ii) at least one platelet function altering agent, and
- iii) at least one serum homocysteine lowering agent.

25 As used herein, physiological mode of action refers to the way in which an active principal exerts its activity on the body of a patient.

Current clinical practice is to treat individual risk factors as they present themselves in any given person. Thus, under current clinical practice, individuals presenting clinical risk
30 factors of cardiovascular disease are treated to return the risk factors (e.g. blood pressure or lipid level) to the so-called normal value, but no lower, by the application of one of many active principals known in the art.

Preferably the formulation has active principals from two of the three categories, i), ii) and iii). More preferably the formulation has active principals from categories i) and ii). Most preferably the formulation comprises active principals from all three categories, i), ii), iii). Optionally the formulation comprises more than one active principal from one or more of
5 the three categories.

The diuretic, the beta blocker, the ACE inhibitor, the angiotensin II receptor antagonist and the calcium channel blocker are preferably those referred to above, preferably in the doses referred to above. Similarly the lipid-regulating agent, the platelet function altering agent,
10 and the serum homocysteine lowering agent are preferably those referred to above, preferably in the dose referred to above.

Under current clinical practice for the use of blood pressure lowering agents, such a formulation in, for example, a single dosage form would not be considered useful given the
15 clinical practice of only providing an additional blood pressure reducing active principal if a first blood pressure reducing active principal, or at most two such drugs in combination, fails to provide the desired lowering of blood pressure. The present inventors have demonstrated that the effect of different classes of the blood pressure reducing active principals act independently and therefore combinations of two or more blood pressure
20 reducing active principals in a single dose produce an additive effect, greatly improving efficacy. Moreover the use of lipid-regulating, platelet function altering and serum homocysteine altering agents in combination with blood pressure lowering agents to reduce a person's overall risk of cardiovascular disease runs contrary to current clinical practice.

25

It will be understood that providing a formulation where the dose of a blood pressure lowering agent is below the lower therapeutic dose for the blood pressure lowering agent is contrary to the art. The lower therapeutic dose for any given blood pressure lowering agent is readily determinable by the skilled addressee by reference to the British National
30 Formulary of March 2000 in common use in the country of this patent at the time of writing.

There is further provided a formulation comprising active principals from at least two of the following three categories:

- i) at least one blood pressure lowering agent,
 - ii) at least one platelet function altering agent, and
 - 5 iii) at least one serum homocysteine lowering agent,
- wherein the dose of the blood pressure lowering agent, if present, is below the lower therapeutic dosage for the blood pressure lowering agent.

Alternatively there is provided a formulation comprising at least one blood pressure
10 lowering agent and active principals from at least one of the following three categories:

- i) at least one lipid-regulating agent,
 - ii) at least one platelet function altering agent, and
 - iii) at least one serum homocysteine lowering agent,
- wherein the dose of the blood pressure lowering agent, if present, is below the lower
15 therapeutic dosage for the blood pressure lowering agent.

Again, the blood pressure reducing agent, the lipid-regulating agent, the platelet function altering agent, and the serum homocysteine lowering agent are preferably those referred to above, preferably in the doses referred to above.

20

In a preferred mode of operation, the present invention relates to treating individuals irrespective of the levels of any risk factors and without any test whatsoever. Preferably selection is based only on a person's age, sex and history of existing cardiovascular disease. In this mode, the avoidance of deleterious side effects is important. Accordingly,
25 it is appropriate for the formulation to contain a lower amount of the blood pressure lowering agent than the normal clinical dose. This is entirely contrary to the state of the art, which provides formulations containing active principals at or around the full therapeutic dose.

30 In another aspect of the invention there is provided a formulation comprising active principals from at least three of the following four categories:

- i) at least one blood pressure lowering agent,
- ii) at least one lipid-regulating agent,

- iii) at least one platelet function altering agent, and
- iv) at least one serum homocysteine lowering agent.

Again, the blood pressure reducing agent, the lipid-regulating agent, the platelet function
5 altering agent, and the serum homocysteine lowering agent are preferably those referred to
above, preferably in the dose referred to above.

Preferably, the formulation contains a dose of a blood pressure lowering agent which is
about half the recommended dose at the lower end of the recommended therapeutic range
10 for the blood pressure lowering agent.

Most preferably, the formulation comprises:

- i) about 12.5 mg hydrochlorothiazide, about 25 mg atenolol, and about 5 mg
enalapril as blood pressure lowering agents,
- 15 ii) about 10 mg atorvastatin as a lipid-regulating agent,
- iii) about 75 mg aspirin as a platelet function altering agent, and
- iv) about 0.8 mg folic acid as a serum homocysteine lowering agent.

Alternatively, the formulation comprises:

- 20 i) about 12.5 mg hydrochlorothiazide, about 25 mg atenolol, and about 5 mg
enalapril as blood pressure lowering agents,
- ii) about 10-20 mg simvastatin as a lipid-regulating agent,
- iii) about 75 mg aspirin as a platelet function altering agent, and
- iv) about 0.8 mg folic acid as a serum homocysteine lowering agent.

25

Alternatively the formulation used in the method of the invention comprises:

- i) about 12.5 mg hydrochlorothiazide, about 25 mg atenolol, and about 2.5mg
amlodipine maleate as blood pressure lowering agents,
- ii) about 10-20 mg simvastatin as lipid-regulating agent,
- 30 iii) about 75 mg aspirin as platelet function altering agent, and
- iv) about 0.8 mg folic acid as serum homocysteine lowering agent.

Alternatively the formulation used in the method of the invention comprises:

- i) about 12.5 mg hydrochlorothiazide, about 2.5mg amlodipine maleate, and about 5 mg enalapril as blood pressure lowering agents,
- ii) about 10-20 mg simvastatin as lipid-regulating agent,
- iii) about 75 mg aspirin as platelet function altering agent, and
- 5 iv) about 0.8 mg folic acid as serum homocysteine lowering agent.

In a still further aspect of the invention, there is provided the use of active principals from two or more of the following three categories:

- i) at least one blood pressure lowering agent,
- 10 ii) at least one lipid-regulating agent, and
- iii) at least one serum homocysteine lowering agent,

with or without at least one platelet function altering agent, for the manufacture of a formulation for administration to an individual without measuring, or if measured regardless of the level of, one or more of the risk factors of cardiovascular disease selected
15 from blood pressure, serum cholesterol, serum homocysteine and platelet function.

Alternatively, there is provided the use of at least one blood pressure lowering agent and at least one active principal from at least one of the following two categories:

- i) at least one lipid-regulating agent, and
- 20 ii) at least one serum homocysteine lowering agent,

with or without at least one platelet function altering agent, for the manufacture of a formulation for administration to an individual without measuring, or if measured regardless of the level of, one or more of the risk factors of cardiovascular disease selected from blood pressure, serum cholesterol, serum homocysteine and platelet function.

25

The formulation of the present invention can be administered by oral or parenteral routes, including intravenous, intramuscular, subcutaneous, transdermal (including patches), airway (aerosol), rectal and topical (including buccal and sublingual) administration. Preferably the formulation of the present invention is provided in a form suitable for oral
30 administration. For oral administration, the formulation of the present invention is preferably in the form of a tablet, a capsule, a pill, a powder, granules, a solution, or a suspension.

Tablets for oral use may include the components mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and
5 lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate, glyceryl distearate, cellulose acetate phthalate, hydroxypropylcellulose phthalate, polyvinylacetate phthalate, methylmethacrylate
10 polymer, a polymer mixture such as Eudragit[®], a cellulose derivative, zein, wax or similar material, or any other dissolvable coat, to delay absorption in the gastrointestinal tract.

Capsules for oral use include hard gelatin capsules in which the components are mixed with a solid diluent, and soft gelatin capsules wherein the components are mixed with
15 water or an oil such as peanut oil, liquid paraffin or olive oil. The components may be compartmentalised within a capsule to prevent contact during storage.

Preferably one or more of the active principals is enteric coated before tableting or encapsulation. Preferably the platelet function altering agent, in particular aspirin, consists
20 of enteric coated beads or granules before tableting or encapsulation. Preferably the whole tablet or capsule is enteric coated. Preferably the enteric coating material comprises cellulose acetate phthalate, hydroxypropylcellulose phthalate, polyvinylacetate phthalate, methylmethacrylate polymer or a polymer mixture such as Eudragit[®].

Preferably one or more of the active principals is delay-release coated before tableting or encapsulation. Preferably the platelet function altering agent, in particular aspirin, consists
25 of delay-release coated beads or granules before tableting or encapsulation. Preferably the whole tablet or capsule is delay-release coated. Preferably the delay-release coating material comprises cellulose acetate phthalate, hydroxypropylcellulose phthalate,
30 polyvinylacetate phthalate, methylmethacrylate polymer, a polymer mixture such as Eudragit[®], a cellulose derivative, zein, glyceryl monostearate or glyceryl distearate.

Preferably the delay-release tablet is formed from a matrix comprising wax or similar material. Alternatively, the delay-release tablet is an erodable tablet formed from a cellulose derivative or similar material. Alternatively, the delay-release tablet is coated with a dissolvable coat.

5

The desired dose is preferably presented once daily, but may be dosed as two, three, four or more sub-doses administered at appropriate intervals throughout the day. Preferably the active principals are present in the tablet, capsule, pill, powder, granules, solution, or suspension in amounts suitable for administration once, twice, or three times per day.

- 10 More preferably the active principals are present in the tablet, capsule, pill, powder, granules, solution, or suspension in amounts suitable for administration once per day.

All preferred dosages are calculated to be at levels optimising the ratio of benefit to hazard, i.e. the ratio of reduction of the risk of cardiovascular disease to the risk of adverse effects

- 15 of the administered agent.

Preferably the formulation is used as a medicament. More preferably the formulation is used as a medicament for the prevention of cardiovascular disease. Most preferably the formulation is used as a medicament for the prevention of ischaemic heart disease.

- 20 Alternatively, most preferably the formulation is used as a medicament for the prevention of stroke or transient ischaemic attack.

Preferably the formulation is used in men and women above a specified age for the reduction in the risk of cardiovascular disease. Alternatively the formulation is used in

25 men and women with an estimated risk of cardiovascular disease above a specified level, wherein the risk is determined by measurement of risk factors used in conjunction with a person's age and sex. The formulation is also used in persons with a clinical history of coronary artery disease or cardiovascular disease irrespective of age or the values of risk factors.

30

Preferably the use of the formulation of the present invention reduces the risk of cardiovascular disease by at least 80%.

The present invention further provides the use of the formulation of the present invention for the manufacture of a medicament for the prevention of cardiovascular disease, preferably the manufacture of a medicament for the prevention of ischaemic heart disease or stroke. Preferably the medicament is used in men and women above specified ages for the reduction in the risk of cardiovascular disease. Alternatively the medicament is used in men and women with an estimated risk of cardiovascular disease above a specified level, wherein the risk is determined by measurement of risk factors used in conjunction with a person's age and sex.

- 10 The present invention further provides a method of preparing the formulation of the present invention, comprising the steps of:
- i) mixing the two or more active principals optionally with one or more pharmaceutically acceptable excipients, and
 - 15 ii) forming the mixture into a tablet, a capsule, a pill, a powder, granules, a solution, or a suspension suitable for oral administration to a patient.

Brief Description of the Drawings

Figure 1 is a graph showing the relative risk (95% confidence limits) of stroke according to blood pressure (reference 1). Both vertical and horizontal axes are plotted on logarithmic scales.

Figure 2 is a graph showing the relative risk (95% confidence limits) of ischaemic heart disease (IHD) according to blood pressure (reference 1). Both vertical and horizontal axes are plotted on logarithmic scales.

Figure 3 is a graph showing the mortality (95% confidence limits) from ischaemic heart disease according to serum cholesterol (reference 2). Both vertical and horizontal axes are plotted on logarithmic scales.

Figure 4 is a graph showing the relative risk (95% confidence limits) of ischaemic heart disease according to serum homocysteine (reference 3). Both vertical and horizontal axes are plotted on logarithmic scales.

Figure 5 is a graph showing the relative risk (95% confidence limits) of ischaemic heart disease according to platelet aggregation (reference 4). The vertical axis is plotted on a logarithmic scale.

5

Figure 6 is a bar chart depicting the deaths from cardiovascular disease above and below the age of 55 for men and for women.

Figure 7 is a graph showing the relative distributions of diastolic blood pressure (in mmHg) in persons who subsequently die from a stroke and in persons of the same age who do not subsequently die from a stroke (If the false positive rate (FPR) is 5%, then the detection rate (DR) is 15%).

Figure 8 is a graph showing the relative distributions of diastolic blood pressure (in mmHg) in persons who subsequently die from ischaemic heart disease and in persons of the same age who do not subsequently die from ischaemic heart disease (If the false positive rate (FPR) is 5%, then the detection rate (DR) is 13%).

Figure 9 is a graph showing the relative distributions of serum cholesterol (in mmol/l) in persons who subsequently die from ischaemic heart disease and in persons of the same age who do not subsequently die from ischaemic heart disease (If the false positive rate (FPR) is 5%, then the detection rate (DR) is 15%).

For each of the factors that affect the risk of heart disease and stroke and that can be favourably altered by drug therapy (blood pressure, serum cholesterol, serum homocysteine and platelet function), the relationships with heart disease and stroke are continuous across the range of values in Western populations. The higher the value of the risk factor, the greater is the risk of heart disease and stroke; an increased risk is not confined to persons with unusually high values of the risk factors. For each of the four risk factors, this continuous proportionate relationship has been established by two classes of evidence.

The first is a series of epidemiological studies in which measurements were made on a large number of persons and the values of the risk factors correlated against the subsequent incidence of heart attacks and stroke. Figures 1 to 5 show five sets of data on the relationships between cardiovascular risk factors and the incidence of ischaemic heart disease or stroke (namely, blood pressure and stroke, blood pressure and ischaemic heart disease, serum cholesterol and ischaemic heart disease, serum homocysteine and ischaemic heart disease, body mass index and ischaemic heart disease). The data are either from single large epidemiological studies or from studies in which the data from several smaller studies have been combined (references 1-4). The study populations have been divided into subgroups (five equal subgroups in three of the five relationships shown) according to ranked values of the risk factor, as shown on the horizontal axes. Incidence, on the vertical axes, is plotted on a logarithmic (or proportional) scale. In each case the relationship is well described by a straight line, and in Figures 1 to 4 the 95% confidence intervals on each of the estimates of incidence are inconsistent with a relationship that is markedly non-linear. The linear relationship indicates that given a change in one of the risk factors from any point on the distribution is associated with a constant proportionate change in the risk of heart disease and stroke.

The second class of evidence is randomised controlled trials in which medication was given to lower the risk factors. Randomised trials have shown that drugs that lower blood pressure produced the same proportionate reduction in the incidence of heart attacks and stroke, irrespective of whether the starting blood pressure was high or average (reference 5). Similarly, randomised trials have shown that drugs that lower serum cholesterol have produced the same proportionate reduction in the incidence of heart attacks and stroke, irrespective of whether the starting concentration of serum cholesterol was high or average (references 6-7). Randomised trials have shown that aspirin reduces the incidence of heart attacks and stroke in both high risk and low risk persons (reference 8) (platelet function was not measured in the aspirin trials). For serum homocysteine no randomised trials are yet available, but evidence is available on persons with different genetic disorders that increase serum homocysteine concentration to varying extents; the increase in risk of cardiovascular disease in the different disorders is commensurate with the increase in serum homocysteine (references 3, 9).

- Because of this continuous proportionate relationship between each of these risk factors and the incidence of ischaemic heart disease and stroke, it would be appropriate to alter all four of them in a person whose risk is high for any reason - a particularly high blood pressure for example, some genetic predisposition (recognised or unrecognised), or simply
- 5 increasing age. The decision that preventive treatment in an individual is worthwhile should be based on the person's overall level of risk of a heart attack or stroke, not on the level of a particular risk factor. Because of the constant proportionate relationship, the benefit will be greater in those whose risk is greater. The preferred approach therefore is to use all these agents to lower risk in persons whose existing overall risk is above a
- 10 specified level. There is a need for a treatment strategy and a formulation that will combine the benefits of all of them, while minimising the occurrence of adverse effects (thereby increasing the potency: hazard ratio), and for the formulation to be available on a wide scale to individuals above a specified risk of having a major cardiovascular episode.
- 15 As stated above, the classical cardiovascular risk factors (blood pressure, serum cholesterol, serum homocysteine) are poor screening tests in discriminating between persons who do and do not develop cardiovascular disease. A more discriminatory determinant of risk is age: the incidence of myocardial infarction and stroke doubles with every eight years of advancing age. By contrast, a doubling of risk occurs over a wide
- 20 span of the distributions of the four risk factors (references 3, 4, 11, 12) (approximately from the 5th centile of the distributions to the 50th, or from the 50th to the 95th). Sex is also an important determinant of risk - the incidence in women at any age is about the same as that in men ten years younger. However, the single most important determinant of a person's risk is the presence of existing disease: in a person who has already had a heart
- 25 attack or a stroke, for example, the risk of death from cardiovascular disease is about 5% per year, irrespective of age, sex, or the values of the risk factors.

- The formulation of the present invention contains various components all designed to reduce the risk of cardiovascular disease by changing different predisposing risk factors.
- 30 The formulation is prepared in doses that maximise efficacy and minimise adverse effects. Preferably the formulation is offered to all persons above a certain age or risk cut-off. The start of treatment could be determined firstly by a person's history of existing disease: any person with a history of previous myocardial infarction or angina, or a previous stroke or

transient ischaemic attack, irrespective of age, sex, or the values of the risk factors, would be at sufficient risk to take the integrated formulation. In persons with no history of past disease, the start of treatment could be determined simply by a person's age and sex so that all men above a specified age (say 55 years) would take the integrated formulation each day and women could follow the same strategy but start at an older age (say at age 65 years). Alternatively, treatment could begin when a person's annual risk of ischaemic heart disease and stroke, calculated from their age, sex, and easily measurable risk factors (for example smoking, blood pressure and body mass index) was above a specified value. Such a policy would be substantially more effective than the current practice of using pharmacological agents specific for a single risk factor and doing so only in individuals with high values of that risk factor or in individuals who have already suffered a major cardiovascular episode. The proposed new approach also takes into account, where current practice does not, that a history of previous cardiovascular disease and, in healthy persons, age are far more discriminatory measures of high risk than any of the cardiovascular risk factors.

Table 3 shows the risk factors altered by each of these drugs, the amount by which each one is changed on average by the preferred dosage, and the resulting expected reduction in the risks of ischaemic heart disease and stroke. Table 3 also shows that all the drugs in combination reduce the risk of ischaemic heart disease by an estimated 88% and of stroke by an estimated 86%. This combined estimate is based on the fact that the effects on the four different risk factors are unrelated and so the expected effects of changing each one will be independent of each other. This expectation is supported by two classes of evidence. First, epidemiological studies (in which the values of the risk factors were measured in many thousands of persons and the distribution of values examined in those who subsequently died of heart disease and stroke and those who did not) have shown that blood pressure, serum cholesterol, platelet function, and serum homocysteine are largely independent of each other in relation to the risk of cardiovascular disease (references 2, 3, 6, 218). For example the ratio of the risk of a disease event in persons with high blood pressure and the risk in persons with low blood pressure is similar, irrespective of the values of serum cholesterol and other risk factors. Second, some randomised clinical trials have used combinations of two of the drugs (for example beta blockers and aspirin) in patients with ischaemic heart disease and have shown that the effects are independent (that

is, the relative risk in patients who took two drugs (compared with the risk in those who took none) was similar to the relative risk in persons taking one of the drugs multiplied by the relative risk in persons taking the other drug). Accordingly, the effect of the different drugs in combination in Table 3 has been calculated by multiplying the effects of each as shown in footnotes h and j.

Drug	Example (daily dose)	Associated physiological variable (reduction produced by drug)	Expected reduction in risk of:	
			ischaemic heart disease	stroke
Thiazide diuretic	Hydrochlorothiazide (12.5 mg)	Blood pressure (12 mmHg diastolic) ^a	43% ^b	63% ^b
Beta blocker	Atenolol (25 mg)			
ACE inhibitor	Enalapril (5 mg)			
Statin	Atorvastatin (10 mg)	Serum cholesterol (1.8 mmol/l) ^c	61% ^d	50% ^d
Aspirin	Aspirin (75 mg)	Platelet aggregation	38% ^e	15% ^e
Folic acid	Folic acid (0.8 mg)	Plasma/serum homocysteine (3 µmol/l) ^f	15% ^g	10% ^g
All drugs in combination			88% ^h	86% ^j

Table 3 - The constituent drugs in the proposed combined formulation, the cardiovascular risk factors that each alter, the amount by which each factor would be changed, and the resulting expected reduction in risk of ischaemic heart disease and stroke.

^a Estimate obtained by us from an analysis of the blood pressure reduction according to dose in 187 randomised placebo controlled trials of thiazide or thiazide-like diuretics, beta-blockers and ACE inhibitors (references 13-199).

^b Reduction in risk to be expected from the blood pressure reduction of 12 mmHg diastolic, from published analyses of cohort studies and randomised controlled trials of blood pressure and ischaemic heart disease and stroke (references 1,5).

^c From published randomised placebo controlled trials of atorvastatin (reference 200).

^d The reduction in risk to be expected from the serum cholesterol reduction of 1.8 mmol/l, from published analyses of cohort studies and randomised controlled trials of serum cholesterol and ischaemic heart disease, and of randomised controlled trials of serum cholesterol reduction and stroke (references 6, 201, 202).

^e Estimate obtained by us from an analysis of the results of 14 randomised controlled trials of aspirin in dosage of 50-100 mg daily and the incidence of ischaemic heart disease and stroke (references 203-216).

^f A meta-analysis of published randomised controlled trials of folic acid in doses between 1 mg and 5 mg showed that the maximum reduction in plasma homocysteine is 3 µmol/l and that this maximum reduction is produced by a folic acid dose of 1 mg (reference 217); an

unpublished randomised controlled trial performed by us has suggested that a folic acid dose of 0.8 mg is the lowest dose that produces this maximum reduction in homocysteine.

^g The reduction in risk to be expected from the reduction in plasma homocysteine of 3 $\mu\text{mol/l}$ from the results of cohort studies of homocysteine and cardiovascular disease (references 3, 9).

^h $100\% - [(100\% - 43\%) \times (100\% - 61\%) \times (100\% - 38\%) \times (100\% - 15\%)] = 88\%$.

^j $100\% - [(100\% - 63\%) \times (100\% - 50\%) \times (100\% - 15\%) \times (100\% - 10\%)] = 86\%$.

Table 4 shows estimates of the prevalence of adverse effects from each of the medications when taken in the preferred dose (shown as the difference in prevalence between treated and placebo groups in randomised trials). The dose of each medication has been chosen to maximise the ratio of benefit to hazard. It is recognised that some persons taking a combination of six drugs would develop adverse effects that were unacceptable. The adverse effects attributable to each of the component medications would be made clear to persons taking the combined formulation and alternative formulations omitting one or more of the component ingredients, with or without a substitute ingredient, would be available for persons unable to tolerate one component.

Drug	Example (daily dose)	Commonest adverse effects	Prevalence of any adverse effect in randomised trials (treated minus control)	Prevalence of serious adverse effects (those that warranted withdrawal from randomised trial) (treated minus control)
Thiazide diuretic	Hydrochlorothiazide (12.5 mg)	dizziness, impotence, nausea	1.4% ^a	0.1% ^a
Beta blocker	Atenolol (25 mg)	cold extremities, fatigue, dizziness	5.6% ^a	0.9% ^a
ACE inhibitor	Enalapril (5 mg)	cough	2.1% ^a	0.2% ^a
Statin	Atorvastatin (10 mg)	-	0.1%	< 0.1%
Aspirin	Aspirin (75 mg)	bleeding, indigestion	1.8% ^b	0.7% ^b (mainly rectal or urinary bleeding)
Folic acid	Folic acid (0.8 mg)	-	< 0.1%	< 0.1%

Table 4 - The estimated prevalence of adverse effects of each of the six drugs to be included in the integrated formulation

^a Estimate obtained by us from an analysis of the prevalence of adverse effects according to dose in 187 randomised placebo controlled trials of thiazide diuretics, beta-blockers and ACE inhibitors (references 13-199).

5 ^b Estimate obtained by us from an analysis of the prevalence of adverse effects in 14 randomised placebo controlled trials of aspirin in dosage between 50 and 100 mg (references 203-216).

- 10 The doses of the first three drugs listed in Tables 3 and 4 (the drugs used to lower blood pressure) are half the present standard (or recommended) dose. Table 5 shows the reduction in blood pressure and in the incidence of ischaemic heart disease and stroke, and the prevalence of adverse effects, from using half standard dose (as in Tables 3 and 4) and from using the present standard (or recommended) dose. There is little loss of efficacy
- 15 using half standard dose, but the prevalence of adverse effects is reduced by almost half. In other words, the ratio of benefit to hazard is greater. The preferred dose of aspirin is the dose generally used in the prevention of cardiovascular disease (75 mg/day); this is much less than the dose necessary to relieve pain.

	Half standard dose (preferred dose)	Standard dose
Reduction in diastolic blood pressure	12 mmHg	15 mmHg
Proportionate reduction in incidence of:		
ischaemic heart disease	43%	50%
stroke	63%	71%
Prevalence of adverse effects	9%	16%

20

Table 5 - The combined effect of three drugs that lower blood pressure (a thiazide diuretic, a beta blocker and an ACE inhibitor) in lowering blood pressure, and reducing the incidence of ischaemic heart disease and stroke, together with the combined prevalence of adverse effects, according to whether the drugs are given in half standard

25 dose or standard dose.

25

Estimates were obtained by us from an analysis of the blood pressure reduction and prevalence of adverse effects according to dose in 187 randomised placebo controlled trials of thiazide diuretics, beta-blockers and ACE inhibitors (references 13-199). The

30 corresponding reductions in incidence of ischaemic heart disease and stroke are those to be expected from the blood pressure reductions, from published analyses of cohort studies and

randomised controlled trials of blood pressure and ischaemic heart disease and stroke (references 1, 5).

It will be understood that the present invention has been described above by way of
5 example only. The examples are not intended to limit the scope of the invention. Various
modifications and embodiments can be made without departing from the scope of the
invention, which is defined by the following claims only.

References

1. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, et al. Blood pressure, stroke and coronary heart disease. Part 1, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990;335:765-74
2. Neaton JD, Wentworth D. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. *Arch Intern Med* 1992;152:56-64
3. Wald NJ, Watt HC, Law MR, Weir DG, McPartlin J, Scott JM. Homocysteine and ischaemic heart disease: results of a prospective study with implications on prevention. *Arch Intern Med* 1997
4. Law MR, Morris JK, Wald NJ. Environmental tobacco smoke exposure and ischaemic heart disease: an evaluation of the evidence. *BMJ* 1997;315:973-88
5. Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, et al. Blood pressure, stroke and coronary heart disease. Part 2, short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet* 1990;335:827-38
6. Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *BMJ* 1994;308:367-72
7. Scandinavian Simvastatin Survival Study Group. Baseline serum cholesterol and treatment effect in the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1995;345:1274-5
8. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy-I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;308:81-106
9. Law MR. Lowering heart disease risk with cholesterol reduction: evidence from observational studies and clinical trials. *European Heart Journal Supplements* 1999; 1 (Suppl S): S3-S8
10. Wald NJ, Hackshaw AK, Frost CD. When can a risk factor be used as a worthwhile screening test? *BMJ* 1999;319:1562-5
11. Stamler J, Stamler R, Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks. *Arch Intern Med* 1993;153:598-615

12. Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? *JAMA* 1986;256:2823-8
13. Petersen JR, Drabaek H, Gleeurup G, Mehlsen J, Petersen LJ, Winther K. ACE Inhibition with spirapril improves diastolic function at rest independent of vasodilation during treatment with spirapril in mild to moderate hypertension. *Angiology* 1996;47:233-40
14. Burris JF, Weir MR, Oparil S, Weber M, Cady WJ, Stewart WH. An assessment of diltiazem and hydrochlorothiazide in hypertension. *JAMA* 1990;263:1507-12
15. Scholze J, Breitstadt A, Cairns V, Bauer B, Bender N, Priestley, et al. Ramipril and hydrochlorothiazide combination therapy in hypertension: a clinical trial of factorial design. *J Hypertens* 1993;11:217-21
16. Frei M, Küster L, von Krosigk PG, Koch H, Küppers. Moxonidine and hydrochlorothiazide in combination: a synergistic antihypertensive effect. *J Cardiovasc Pharmacol* 1994;24(Suppl 1):S25-S28
17. Goldberg MR, Rockhold FW, Offen WW, Dornseif BE. Dose-effect and concentration-effect relationships of pinacidil and hydrochlorothiazide in hypertension. *Clin Pharmacol Ther* 1989;46:208-18
18. Muiesan G, Agabiti-Rosei E, Buoninconti R, Cagli V, Carotti A, Corea L, et al. Antihypertensive efficacy and tolerability of captopril in the elderly: comparison with hydrochlorothiazide and placebo in a multicentre, double-blind study. *J Hypertens* 1987;5 (Suppl 5):S599-S602
19. Pool PE, Applegate WB, Woehler T, Sandall P, Cady WJ. A randomized, controlled trial comparing diltiazem, hydrochlorothiazide, and their combination in the therapy of essential hypertension. *Pharmacotherapy* 1993;13:487-93
20. Wing LMH, Arnolda LF, Harvey PJ, Upton J, Molloy D, Bune AJC, et al. Lacidipine, hydrochlorothiazide and their combination in systolic hypertension in the elderly. *J Hypertens* 1997;15:1503-10
21. Chalmers JP, Morris MJ, Wing LMH, Cain MD, West MJ, Graham JR, et al. Effects of enalapril and hydrochlorothiazide on blood pressure, renin-angiotensin system, and atrial natriuretic factor in essential hypertension: a double blind factorial cross-over study. *Aust NZ J Med* 1986;16:475-80
22. Chalmers JP, Korner PI, Tiller DJ, Bune AJ, Steiner JD, West MJ, et al. Double-

- blind factorial trial of prindolol and hydrochlorothiazide in hypertension. *Med J Aust* 1976;1:650-3
23. Chalmers J, Horvath J, Tiller D, Bune A. Effects of timolol and hydrochlorothiazide on blood-pressure and plasma renin activity. *Lancet* 1976;2:328-31
 24. McCorvey E, Wright JT, Culbert JP, McKenney JM, Proctor JD, Annett MP. Effect of hydrochlorothiazide, enalapril, and propranolol on quality of life and cognitive and motor function in hypertensive patients. *Clinical Pharmacy* 1993;12:300-5
 25. Myers MG, de Champlain J. Effects of atenolol and hydrochlorothiazide on blood pressure and plasma catecholamines in essential hypertension. *Hypertension* 1983;5:591-6
 26. Jounela AJ, Lilja M, Lumme J, Mörlin C, Hoyem A, Wessel-aas T, et al. Relation between low dose of hydrochlorothiazide, antihypertensive effect and adverse effects. *Blood Press* 1994;3:231-5
 27. Pool J, Cushman WC, Saini RK, Nwachuku CE, Battikha JP. Use of the factorial design and quadratic response surface models to evaluate the fosinopril and hydrochlorothiazide combination therapy in hypertension. *Am J Hypertens* 1997;10:117-23
 28. Canter D, Frank GJ, Knapp LE, Phelps M, Quade M, Texter M. Quinapril and hydrochlorothiazide combination for control of hypertension: assessment by factorial design. *J Hum Hypertens* 1994;8:155-62
 29. Frishman WH, Bryzinski BS, Coulson LR, DeQuattro VL, Vlachakis ND, Mroczek WJ, et al. A multifactorial trial design to assess combination therapy in hypertension. *Arch Intern Med* 1994;154:1461-9
 30. Zachariah PK, Messerli FH, Mroczek W. Low-dose bisoprolol/hydrochlorothiazide: an option in first-line, antihypertensive treatment. *Clin Ther* 1993;15:779-87
 31. Chrysant SG. Antihypertensive effectiveness of low-dose lisinopril-hydrochlorothiazide combination. *Arch Intern Med* 1994;154:737-43
 32. Fernández M, Madero R, González D, Camacho P, Villalpando J, Arriaga J. Combined versus single effect of fosinopril and hydrochlorothiazide in hypertensive patients. *Hypertension* 1994;23 (Suppl I):I-207-10

33. Lacourcière Y, Arnott W. Placebo-controlled comparison of the effects of nebivolol and low-dose hydrochlorothiazide as monotherapies and in combination on blood pressure and lipid profile in hypertensive patients. *J Hum Hypertens* 1994;8:283-8
34. Pordy RC. Cilazapril plus hydrochlorothiazide: improved efficacy without reduced safety in mild to moderate hypertension. *Cardiology* 1994;85:311-22
35. Weir MR, Weber MA, Punzi HA, Serfer HM, Rosenblatt S, Cady WJ. A dose escalation trial comparing the combination of diltiazem SR and hydrochlorothiazide with the monotherapies in patients with essential hypertension. *J Hum Hypertens* 1992;6:133-8
36. Brown CL, Backhouse CI, Grippat JC, Santoni JP. The effect of perindopril and hydrochlorothiazide alone and in combination on blood pressure and on the renin-angiotensin system in hypertensive subjects. *Eur J Clin Pharmacol* 1990;39:327-32
37. Chrysant SG, Fagan T, Glazer R, Kriegman A. Effects of benazepril and hydrochlorothiazide, given alone and in low- and high-dose combinations, on blood pressure in patients with hypertension. *Arch Fam Med* 1996;5:17-24
38. Frishman WH, Burris JF, Mroczek WJ, Weir MR, Alemayehu D, Simon JS, et al. First-line therapy option with low-dose bisoprolol fumarate and low-dose hydrochlorothiazide in patients with stage I and stage II systemic hypertension. *J Clin Pharmacol* 1995;35:182-8
39. Kayanakis JG, Baulac L. Comparative study of once-daily administration of captopril 50mg, hydrochlorothiazide 25mg and their combination in mild to moderate hypertension. *Br J Clin Pharmacol* 1987;23 (Suppl 1):89S-92S
40. Moser M, Abraham PA, Bennett WM, Brachfeld N, Goodman RP, McKenney JM, et al. The effects of benazepril, a new angiotensin-converting enzyme inhibitor, in mild to moderate essential hypertension: a multicenter study. *Clin Pharmacol Ther* 1991;49:322-9
41. Persson B, Stimpel M. Evaluation of the antihypertensive efficacy and tolerability of moexipril, an new ACE inhibitor, compared to hydrochlorothiazide in elderly patients. *Eur J Clin Pharmacol* 1996;50:259-64
42. Jueng C, Halperin AK, Hasmimoto F, Callender K. Nifedipine GITS and hydrochlorothiazide in essential hypertension. *J Clin Hypertens* 1987;3:695-703

43. Scholz D, Schwille PO, Sigel A. Double-blind study with thiazide in recurrent calcium lithiasis. *J Urol* 1982;128:903-7
44. Materson BJ, Oster JR, Michael UF, Bolton SM, Burton ZC, Stambaugh JE, et al. Dose response to chlorthalidone in patients with mild hypertension. *Clin Pharmacol Ther* 1978;24:192-8
45. Morledge JH, Ettinger B, Aranda J, BcBarron F, Barra P, Gorwit J, et al. Isolated systolic hypertension in the elderly. A placebo-controlled, dose-response evaluation of chlorthalidone. *J Am Geriatr Soc* 1986;34:199-206
46. Bateman DN, Dean CR, Mucklow JC, Bulpitt CJ, Dollery CT. Atenolol and chlorthalidone in combination for hypertension. *Br J Clin Pharmacol* 1979;7:357-63
47. Erwtelman TM, Nagelkerke N, Lubsen J, Koster M, Dunning AJ. β Blockade, diuretics, and salt restriction for the management of mild hypertension: a randomised double blind trial. *BMJ* 1984;289:406-9
48. Ferrara LA, de Simone G, Mancini M, Fasano ML, Pasanisi F, Vallone G. Changes in left ventricular mass during a double-blind study with chlorthalidone and slow-release nifedipine. *Eur J Clin Pharmacol* 1984;27:525-8
49. McFate Smith WM, Feigal DW, Furberg CD, Greenlick M, Kuller L, Perry HM, et al. Use of diuretics in treatment of hypertension in the elderly. *Drugs* 1986;31:154-64
50. Moser M. Low-dose diuretic therapy for hypertension. *Clin Ther* 1986;8:554-62
51. Salvetti A, Magagna A, Innocenti P, Ponzanelli F, Cagianelli A, Cipriani M, et al. The combination of chlorthalidone with nifedipine does not exert an additive antihypertensive effect in essential hypertensives: a crossover multicenter study. *J Cardiovasc Pharmacol* 1991;17:332-5
52. Wing LMH, West MJ, Graham JR, Chalmers JP. Long-acting and short-acting diuretics in mild essential hypertension. *Clin Exp Hypertens* 1982;A4:1429-41
53. Bradley K, Flack JM, Belcher J, Elmer P, Miller P, Grimm R. Chlorthalidone attenuates the reduction in total cholesterol and small, dense LDL cholesterol subclass associated with weight loss. *Am J Hypertens* 1993;6:636-9
54. Cranston WI, Juel-Jensen BE. The effects of spironolactone and chlorthalidone on arterial pressure. *Lancet* 1962;1:1161-4
55. Durel LA, Hayashi PJ, Weidler DJ, Schneiderman N. Effectiveness of

- antihypertensive medications in office and ambulatory settings: a placebo-controlled comparison of atenolol, metoprolol, chlorthalidone, verapamil, and an atenolol-chlorthalidone combination. *J Clin Pharmacol* 1992;32:564-70
56. Hall WD, Weber MA, Ferdinand K, Flamenbaum W, Marbury T, Jain AK, et al. Lower dose diuretic therapy in the treatment of patients with mild to moderate hypertension. *J Hum Hypertens* 1994;8:571-5
57. Fiddes R, Blumenthal J, Dawson JE, Dyckman E, Hammond PGS, Harris S, et al. Evaluation of indapamide 1.25mg once daily in elderly patients with mild to moderate hypertension. *J Hum Hypertens* 1997;11:239-44
58. Weidler D, Jallad NS, Curry C, Ferdinand K, Jain AK, Schnaper HW, et al. Efficacious response with lower dose indapamide therapy in the treatment of elderly patients with mild to moderate hypertension. *J Clin Pharmacol* 1995;35:45-51
59. Borghi L, Meschi T, Guerra A, Novarini A. Randomized prospective study of a nonthiazide diuretic, indapamide, in preventing calcium stone recurrences. *J Cardiovasc Pharmacol* 1993;22 (Suppl 6):S78-S86
60. Chalmers JP, Wing LMH, Grygiel JJ, West MJ, Graham JR, Bune AJ. Effects of once daily indapamide and pindolol on blood pressure, plasma aldosterone concentration and plasma renin activity in a general practice setting. *Eur J Clin Pharmacol* 1982;22:191-6
61. Schaller M, Waeber B, Brunner HR. Double-blind comparison of indapamide with a placebo in hypertensive patients treated by practicing physicians. *Clin Exp Hypertens* 1985;A7:985-94
62. Taylor DR, Constable J, Sonnekus M, Milne FJ. Effect of indapamide on serum and red cell cations, with and without magnesium supplementation, in subjects with mild hypertension. *S Afr Med J* 1988;74:272-6
63. Carlsen JE, Køber L, Torp-Pedersen, Johansen P. Relation between dose of bendrofluazide, antihypertensive effect, and adverse biochemical effects. *BMJ* 1990;300:975-8
64. Christiansen C, Christensen MS, Hagen C, Stocklund KE, Transbøl. Effects of natural estrogen/gestagen and thiazide on coronary risk factors in normal postmenopausal women. *Acta Obstet Gynecol Scand* 1981;60:407-412
65. Horvath JS, Caterson RJ, Collett P, Duggin GG, Kelly DH, Tiller DJ. Labetalol

- and bendrofluazide: comparison of their antihypertensive effects. *Med J Aust* 1979;1:626-8
66. Webster J, Dollery CT, Hensby CN. Circulating prostacyclin concentrations may be increased by bendrofluazide in patients with essential hypertension. *Clin Sci* 1980;59 (Suppl 6):125s-128s
67. Wilcox RG. Randomised study of six beta-blockers and a thiazide diuretic in essential hypertension. *BMJ* 1978;2:383-5
68. Fernandez PG, Zachariah PK, Bryant DG, Missan SS. Antihypertensive efficacy of α -methyldopa, chlorothiazide and Supres-150 (α -methyldopa-chlorothiazide). *Can Med Assoc J* 1980;123:284-7
69. Curry CL, Harris R, MacKay JH, Nugent CA, Ryan J, Schnaper, et al. Clinical studies of a new, low-dose formulation of metolazone for the treatment of hypertension. *Clin Ther* 1986;9:47-62
70. McVeigh G, Galloway D, Johnston D. The case for low dose diuretics in hypertension: comparison of low and conventional doses of cyclopenthiazide. *BMJ* 1988;297:95-8
71. Chrysant SG, Chappel C, Farnham J, Levin B, Lueg M, McCluskey D, et al. Antihypertensive and metabolic effects of single and combined atenolol regimens. *J Clin Pharmacol* 1992;32:61-65
72. Ekblom T, Dahlöf B, Hansson L, Lindholm LH, Scherstén B, Wester P. Antihypertensive efficacy and side effects of three beta-blockers and a diuretic in elderly hypertensives: a report from the STOP-Hypertension study. *J Hypertens* 1991;10:1525-9
73. Gostick NK, Mayhew SR, Million R, Sagar D, Suxena SR, Igram DF, et al. A dose-response study of atenolol in mild to moderate hypertension in general practice. *Curr Med Res Opin* 1977;5:179-84
74. Saul P, Jones BP, Edwards KG, Tweed JA. Randomized comparison of atenolol and placebo in the treatment of anxiety: a double-blind study. *Eur J Clin Pharmacol* 1985;28:109-110
75. Tonkin AL, Wing LMH, Russell AE, West MJ, Bune AJC, Morris MJ, et al. Diltiazem and atenolol in essential hypertension: additivity of effects on blood pressure and cardiac conduction with combination therapy. *J Hypertens* 1990;8:1015-8

76. Wing LMH, Chalmers JP, West MJ, Russell AE, Morris MJ, Cain MD. Enalapril and atenolol in essential hypertension: attenuation of hypertensive effects in combination. *Clin Exp Hypertens* 1988;10:119-33
77. Cilliers AJ. Atenolol as primary therapy in previously untreated hypertensives and as an adjuvant to other therapy. *S Afr Med J* 1979;55:321-4
78. Clement DL, De Pue NY, Packet L. Effect of calcium antagonists on ambulatory blood pressure and its variations. *J Cardiovasc Pharmacol* 1987;10 (Suppl 10):S117-S119
79. Houston MC, Burger C, Hays JT, Nadeau J, Swift L, Bradley CA, et al. The effects of clonidine hydrochloride versus atenolol monotherapy on serum lipids, lipid subfractions, and apolipoproteins in mild hypertension. *Am Heart J* 1990;120:172-9
80. Lange-Andersen KL, Ottmann W, Piatkowski W, Green KA. Working ability and exercise tolerance during treatment of mild hypertension. *Int Arch Occup Environ Health* 1985;56:49-55
81. Lyons D, Fowler G, Webster J, Hall ST, Petrie JC. An assessment of lacidipine and atenolol in mild to moderate hypertension. *Br J Clin Pharmacol* 1994;37:45-51
82. Streufert S, DePadova A, McGlynn T, Pogash R, Piasecki M. Impact of β -blockade on complex cognitive functioning. *Am Heart J* 1988;116:311-4
83. Tötterman K, Groop L, Groop P, Kala R, Tolppanen, Fyhrquist F. Effect of beta-blocking drugs on beta-cell function and insulin sensitivity in hypertensive non-diabetic patients. *Eur J Clin Pharmacol* 1984;26:13-7
84. Vanhees L, Fagard R, Lijnen P, Amery A. Effect of antihypertensive medication on endurance exercise capacity in hypertensive sportsmen. *J Hypertens* 1991;9:1063-8
85. Verdecchia P, Gatteschi C, Benemio G, Boldrini F, Guerrieri M, Porcellati C. Duration of the antihypertensive action of atenolol, enalapril and placebo. *Int J Clin Pharmacol Ther Toxicol* 1988;26:570-4
86. Clement DL, Bogaert MG, Pannier R. Effect of beta-adrenergic blockage on blood pressure variation in patients with moderate hypertension. *Eur J Clin Pharmacol* 1977;11:325-7
87. Baez MA, Garg DC, Jallad NS, Weidler DJ. Antihypertensive effect of doxazosin

- in hypertensive patients: comparison with atenolol. *Br J Clin Pharmacol* 1986;21 (Suppl 1):63S-67S
88. Jeffers TA, Webster J, Petrie JC. Atenolol once-daily in hypertension. *Br J Clin Pharmacol* 1977;4:523-7
89. Maclean D, Mitchell ET, Lewis R, Irvine N, McLay S, McEwen J, et al. Comparison of once daily atenolol, nitrendipine and their combination in mild to moderate essential hypertension. *Br J Clin Pharmacol* 1990;29:455-63
90. Van Nueten L, Taylor FR, Robertson JIS. Nebivolol vs atenolol and placebo in essential hypertension: a double-blind randomised trial. *J Hum Hypertens* 1998;12:135-40
91. Petrie C, Jeffers TA, Robb OJ, Scott AK, Webster J. Atenolol, sustained-release oxprenolol, and long-acting propranolol in hypertension. *BMJ* 1980;1:1573-4
92. Wilcox RG, Hampton JR. Comparative study of atenolol, metoprolol, metoprolol durules, and slow-release oxprenolol in essential hypertension. *Br Heart J* 1981;46:498-502
93. Roberts DH, Tsao Y, MCLoughlin GA, Breckenridge A. Placebo-controlled comparison of captopril, atenolol, labetalol, and pindolol in hypertension complicated by intermittent claudication. *Lancet* 1987;2:650-3
94. Hansson L, Åberg H, Karlberg BE, Westerlund A. Controlled study of atenolol in treatment of hypertension. *BMJ* 1975;2:367-70
95. Broekman CPM, Haensel SM, Ven de Ven LLM, Slob AK. Bisoprolol and hypertension: effects on sexual functioning in men. *J Sex Marital Ther* 1992;18:325-31
96. Davidov ME, Singh SP, Vlachakis ND, Blumenthal JB, Simon JS, Bryzinski JS, et al. Bisoprolol, a once-a-day beta-blocking agent for patients with mild to moderate hypertension. *Clin Cardiol* 1994;17:263-268
97. Tseng C, Chiang F, Hsu K, Tseng Y, Hu W, Chen J, et al. Short-term efficacy and safety of bisoprolol in treatment of patients with mild-to-moderate hypertension - A two-center, double-blind study in Taiwan. *Acta Cardiologica Sinica* 1993;9:155-60
98. Van de Ven LLM, Mouthaan BJ, Hoes MJ. Treatment of hyperventilation syndrome with bisoprolol: a placebo-controlled clinical trial. *J Psychosom Res* 1995;39:1007-13

99. Asmar RG, Kerihuel JC, Girerd XJ, Safar ME. Effect of bisoprolol on blood pressure and arterial hemodynamics in systemic hypertension. *Am J Cardiol* 1991;68:61-4
100. Ameling EH, de Korte DF, Man in 't Veld AJ. Impact of diagnosis and treatment of hypertension on quality of life: a double-blind, randomized, placebo-controlled, cross-over study of betaxolol. *J Cardiovasc Pharmacol* 1991;18:752-60
101. Williams RL, Goyle KK, Herman TS, Rofman BA, Ruoff GE, Hogan LB. Dose-dependent effects of betaxolol in hypertension: a double-blind multicenter study. *J Clin Pharmacol* 1992;32:360-7
102. Salonen JT, Palminteri R. Comparison of two doses of betaxolol and placebo in hypertension: a randomised, double-blind cross-over trial. *Eur J Clin Pharmacol* 1982;23:491-4
103. Jäätelä A, Baandrup S, Houtzagers J, Westergren G. The efficacy of low dose metoprolol CR/ZOK in mild hypertension and in elderly patients with mild to moderate hypertension. *J Clin Pharmacol* 1990;30 (Suppl):S66-S71
104. Landin K, Tengborn L, Smith U. Metformin and metoprolol CR treatment in non-obese men. *J Intern Med* 1994;235:335-41
105. Groop L, Tötterman KJ, Harno K, Gordin A. Influence of beta-blocking drugs on glucose metabolism in hypertensive, non-diabetic patients. *Acta Med Scand* 1983;213:9-14
106. Lepäntalo MJA, Tötterman KJ. Lower limb haemodynamics during antihypertensive treatment with metoprolol and propranolol. *Inter Angiol* 1985;4:225-8
107. MacMahon S, MacDonald GJ, Bernstein L, Andrews G, Blacket RB. Comparison of weight reduction with metoprolol in treatment of hypertension in young overweight patients. *Lancet* 1985;1:1233-6
108. Reybrouck T, Amery A, Fagard R, Jousten P, Lijnen P, Meulepas E. Beta-blockers: once or three times a day? *BMJ* 1978;1:1386-8
109. Vandongen R, Margetts B, Deklerk N, Beilin LJ, Rogers P. Plasma catecholamines following exercise in hypertensives treated with pindolol: comparison with placebo and metoprolol. *Br J Clin Pharmacol* 1986;21:627-32
110. Trafford JAP, Latta D, Little PS, Parsley J, Ankier SI. A multi-centre, placebo controlled comparative study between 200 mg and 400 mg celiprolol in patients

- with mild to moderate essential hypertension. *Curr Med Res Opin* 1989;11:550-6
111. Kimura S, DeQuattro V, Hernandez PH, Lee DD. Effects of celiprolol on plasma renin, aldosterone, norepinephrine and epinephrine in primary hypertension. *Am J Cardiol* 1988;62:751-4
 112. Watson RDS, Stallard TJ, Littler WA. Comparison of once and twice daily administration of acebutolol in hypertension. *Br J Clin Pharmacol* 1980;9:209-12
 113. Van Nueten L, Dupont AG, Vertommen C, Goyvaerts H, Robertson JIS. A dose-response trial of nebivolol in essential hypertension. *J Hum Hypertens* 1997;11:139-44
 114. Himmelmann A, Hedner T, Snoeck E, Lundgren B, Hedner J. Haemodynamic effects and pharmacokinetics of oral *d*- and *l*-nebivolol in hypertensive patients. *Eur J Clin Pharmacol* 1996;51:259-64
 115. Glasscock RJ, Weitzman RE, Bennett CM, Maxwell M, Hamilton B, Winer N, et al. Pindolol: effects on blood pressure and plasma renin activity. *Am Heart J* 1982;104:421-5
 116. Hamilton BP, Hamilton J, Kirkendall WM. Pulmonary function in hypertensive patients treated with pindolol: a report of two studies. *Am Heart J* 1982;104:432-7
 117. Galloway DB, Glover SC, Hendry WG, Logie AW, Petrie JC, Smith MC, et al. Propranolol in hypertension: a dose-response study. *BMJ* 1976;2:140-2
 118. Dargie H, Cleland J, Findlay I, Murray G, McInnes G. Combination of verapamil and beta-blockers in systemic hypertension. *Am J Cardiol* 1986;57:80D-82D
 119. McInnes GT, Findlay IN, Murray G, Cleland JGF, Dargie HJ. Cardiovascular responses to verapamil and propranolol in hypertensive patients. *J Hypertens* 1985;3 (Suppl 3):S219-21
 120. Hudson CFE. An evaluation of once daily long acting propranolol hydrochloride (Inderal LA and Half-Inderal LA) in the treatment of anxiety. A double-blind placebo-controlled general practice study. *Br J Clin Pract* 1988;42:419-26
 121. Pearson RM, Bulpitt CJ, Havard CWH. Biochemical and haematological changes induced by tienilic acid combined with propranolol in essential hypertension. *Lancet* 1979;1:697-9
 122. Moleur P, Peyrieux JC, Luciani J, David D, Boissel JP. Bopindolol in the treatment of moderate hypertension: a dose-response study. *Fundam Clin Pharmacol* 1988;2:431-40

123. Adsett CA, Bellissimo A, Mitchell A, Wilczynski N, Haynes RB. Behavioral and physiological effects of a beta-blocker and relaxation therapy on mild hypertensives. *Psychosom Med* 1989;51:523-6
124. Dupont AG, Vanderniepen P, Bossuyt AM, Jonckheer MH, Six RO. Nadolol in essential hypertension: effect on ambulatory blood pressure, renal haemodynamics and cardiac function. *Br J Clin Pharmacol* 1985;20:93-99
125. Casadei B, Conway J, Coats AJS, Bird R. Antihypertensive effect of carvedilol: a preliminary dose-response study. *Clinical Investigator* 1992;70 (Suppl):S37-S38
126. Dupont AG, Van der Niepen P, Taeymans Y, Ingels M, Piepsz A, Bossuyt AM, et al. Effect of carvedilol on ambulatory blood pressure, renal hemodynamics, and cardiac function in essential hypertension. *J Cardiovasc Pharmacol* 1987;10 (Suppl 11):S130-S136
127. Morgan TO, Morgan O, Anderson A. Effect of dose on trough peak ratio of antihypertensive drugs in elderly hypertensive males. *Clin Exp Pharmacol Physiol* 1995;22:778-80
128. Chrysant SG, Brown RD, Kem DC, Brown JL. Antihypertensive and metabolic effects of a new converting enzyme inhibitor, enalapril. *Clin Pharmacol Ther* 1983;33:741-6
129. Kaski JC, Rosano G, Gavrielides S, Chen L. Effects of angiotensin-converting enzyme inhibition on exercise induced angina and ST segment depression in patients with microvascular angina. *J Am Coll Cardiol* 1987;23:652-7
130. Küppers HE, Jäger BA, Luszick JH, Gräve, Hughes PR, Kaan EC. Placebo-controlled comparison of the efficacy and tolerability of once-daily moxonidine and enalapril in mild-to-moderate essential hypertension. *J Hypertens* 1997;15:93-7
131. Naranjo CA, Kadlec KE, Sanhueza P, Woodley-Remus D, Sellers EM. Enalapril effects on alcohol intake and other consummatory behaviors in alcoholics. *Clin Pharmacol Ther* 1991;50:96-106
132. Simon G, Morioka S, Snyder DK, Cohn JN. Increased renal plasma flow in long-term enalapril treatment of hypertension. *Clin Pharmacol Ther* 1983;34:459-65
133. van Baak MA, Mooij JMV, Wijnen JAG, Tan FS. Submaximal endurance exercise performance during enalapril treatment in patients with essential hypertension. *Clin Pharmacol Ther* 1991;50:221-7

134. Whelton A, Dunne B, Glazer N, Kostis JB, Miller WE, Rector DJ, et al. Twenty-four hour blood pressure effect of once-daily lisinopril, enalapril, and placebo in patients with mild to moderate hypertension. *J Hum Hypertens* 1992;6:325-31
135. Gibbs JSR, Crean PA, Mockus L, Wright C, Sutton G, Fox KM. The variable effects of angiotensin converting enzyme inhibition on myocardial ischaemia in chronic stable angina. *Br Heart J* 1989;62:112-7
136. Gradman AH, Arcuri KE, Goldberg AI, Ikeda LS, Nelson EB, Snively DB, et al. A randomized, placebo-controlled, double-blind, parallel study of various doses of losartan potassium compared with enalapril maleate in patients with essential hypertension. *Hypertension* 1995;25:1345-50
137. Krum H, Viskoper RJ, Lacourciere Y, Budde M, Charlon V. The effect of an endothelin-receptor antagonist, bosentan, on blood pressure in patients with essential hypertension. *N Eng J Med* 1998;338:784-90
138. Forette F, Handfield-Jones R, Henry-Amar M, Fouchard M, Bouchacourt P, Hervy M, et al. Rationale for ACE inhibition in the elderly: treatment of arterial hypertension with enalapril. *Gerontology* 1987;33:9-16
139. Sassano P, Chatellier G, Alhenc-Gelas F, Corvol P, Menard J. Antihypertensive effect of enalapril as first-step treatment of mild and moderate uncomplicated essential hypertension. *Am J Med* 1984;77(suppl 2A):18-22
140. Applegate WB, Cohen JD, Wolfson P, Davis A, Green S. Evaluation of blood pressure response to the combination of enalapril (single dose) and diltiazem ER (four different doses) in systemic hypertension. *Am J Cardiol* 1996;78:51-5
141. Cushman WC, Cohen JD, Jones RP, Marbury TC, Rhoades RB, Smith LK. Comparison of the fixed combination of enalapril/diltiazem ER and their monotherapies in stage 1 to 3 essential hypertension. *Am J Hypertens* 1998;11:23-30
142. Franke H. Antihypertensive effects of candesartan cilexetil, enalapril and placebo. *J Hum Hypertens* 1997;11 (Suppl 2):S61-62
143. Levine JH, Ferdinand KC, Cargo P, Laine H, Lefkowitz M. Additive effects of verapamil and enalapril in the treatment of mild to moderate hypertension. *Am J Hypertens* 1995;8:494-9
144. Salvetti A, Arzilli F. Chronic dose-response curve of enalapril in essential hypertensives. *Am J Hypertens* 1989;2:352-4

145. Holwerda NJ, Fogari R, Angeli P, Porcellati C, Hereng C, Oddou-Stock P, et al. Valsartan, a new angiotensin II antagonist for the treatment of essential hypertension: efficacy and safety compared with placebo and enalapril. *J Hypertens* 1996;14:1147-51
146. Bergstrand R, Herlitz H, Johansson S, Berglund G, Vedin A, Wilhelmsson C, et al. Effective dose range of enalapril in mild to moderate essential hypertension. *Br J Clin Pharmacol* 1985;19:605-11
147. Louis WJ, Workman BS, Conway EL, Worland P, Rowley K, Drummer O, et al. Single-dose and steady-state pharmacokinetics and pharmacodynamics of perindopril in hypertensive subjects. *J Cardiovasc Pharmacol* 1992;20:505-11
148. Luccioni R, Frances Y, Gass R, Gilgenkrantz JM. Evaluation of the dose-effect relationship of perindopril in the treatment of hypertension. *Clin Exp Hypertens* 1989;A11:521-34
149. Myers MG. A dose-response study of perindopril in hypertension: effects on blood pressure 6 and 24h after dosing. *Am J Cardiol* 1996;12:1191-6
150. West JNW, Smith SA, Stallard TJ, Littler WA. Effects of perindopril on ambulatory intra-arterial blood pressure, cardiovascular reflexes and forearm blood flow in essential hypertension. *J Hypertens* 1989;7:97-104
151. Chrysant SG, McDonald RH, Wright JT, Barden PL, Weiss RJ. Perindopril as monotherapy in hypertension: a multicenter comparison of two dosing regimens. *Clin Pharmacol Ther* 1993;53:479-84
152. Overlack A, Adamczak M, Bachmann W, Bönner G, Bretzel RG, Derichs R, et al. ACE-inhibition with perindopril in essential hypertensive patients with concomitant diseases. *Am J Med* 1994;97:126-34
153. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Low-dose captopril for the treatment of mild to moderate hypertension. *Arch Intern Med* 1984;144:1947-53
154. Drayer JIM, Weber MA. Monotherapy of essential hypertension with a converting-enzyme inhibitor. *Hypertens* 1983;5 (Suppl III):III108-13
155. Schoenberger JA, Wilson DJ. Once-daily treatment of essential hypertension with captopril. *J Clin Hypertens* 1986;4:379-87
156. Conway J, Way B, Boon N, Somers V. Is the antihypertensive effect of captopril influenced by the dosage frequency? A study with ambulatory monitoring. *J Hum*

Hypertens 1988;2:123-6

157. Lavessaro G, Ladetto PE, Valente M, Stramignoni D, Zanna C, Assogna G, et al. Ketanserin and captopril interaction in the treatment of essential hypertensives. *Cardiovasc Drugs Ther* 1990;4:119-22
158. Salvetti A, Innocenti PF, Iardella M, Pambianco F, Saba GC, Rossetti M, et al. Captopril and nifedipine interactions in the treatment of essential hypertensives: a crossover study. *J Hypertens* 1987;5 (Suppl 4):S139-S142
159. Salvetti A, Circo A, Raciti S, Gulizia M, Cardillo R, Miceli S, et al. Captopril at 50mg as well as at 100mg once a day reduces blood pressure for up to 24h: a double-blind randomized crossover study in mild to moderate hypertensives. *J Hypertens* 1988;6 (Suppl 4):S666-S668
160. Fernandez PG, Bolli P, Lee C. The 24h blood pressure responses of hypertensives to a once-a-day cilazapril regimen. *Can J Cardiol* 1990;6:53-8
161. Güntzel P, Kobrin I, Pasquier C, Zimlichman R, Viskoper JR. The effect of cilazapril, a new angiotensin converting enzyme inhibitor, on peak and trough blood pressure measurements in hypertensive patients. *J Cardiovasc Pharmacol* 1991;17:8-12
162. Kobrin I, Güntzel P, Viskoper R, Paran E, Zimlichman R. Antihypertensive duration of action of cilazapril in patients with mild to moderate essential hypertension. *Drugs* 1991;41:31-6
163. Krum H, Jackson B, Conway EL, Howes LG, Johnston CI, Louis WJ. Steady-state pharmacokinetics and pharmacodynamics of cilazapril in the presence and absence of cyclopenthiazide. *J Cardiovasc Pharmacol* 1992;20:451-7
164. Lacourcière Y, Leenen F, Rangno R, Spence JD, Lenis JH, Myers MG. Discrepancies between clinic and ambulatory blood pressure responses to cilazapril therapy. *Can J Cardiol* 1994;10:605-10
165. Mroczek WJ, Klein J, Burris JF. Dose-finding study of cilazapril (inhibace) in patients with uncomplicated essential hypertension. *Clin Exp Hypertens* 1991;A13:1415-32
166. Prager G, Klein P, Schmitt M, Prager R. Antihypertensive efficacy of cilazapril 2.5 and 5.0mg once-daily versus placebo on office blood pressure and 24-hour blood pressure profile. *J Cardiovasc Pharmacol* 1994;24 (Suppl 3):S93-S99
167. White WB, McCabe EJ, Hager WD, Schulman P. The effects of the long-acting

- angiotensin-converting enzyme inhibitor cilazapril on casual, exercise and ambulatory blood pressure. *Clin Pharmacol Ther* 1988;**44** (Suppl 3):173-8
168. Poirier L, Pyzyk M, Provencher P, Lacourcière. Comparative effects of 2.5 and 5mg cilazapril versus placebo on daily blood pressure load. *Am J Hypertens* 1991;**4**:913-5
169. DeQuattro V, Lee D. Fixed-dose combination therapy with trandolapril and verapamil SR is effective in primary hypertension. *Am J Hypertens* 1997;**10** (Suppl):138S-145S
170. Veratran Study Group. Effects of verapamil SR, trandolapril, and their fixed combination on 24-h blood pressure. *Am J Hypertens* 1997;**10**:492-9
171. Weir MR, Gray JM, Paster R, Saunders E. Differing mechanisms of action of angiotensin-converting enzyme inhibition in black and white hypertensive patients. *Hypertension* 1995;**26**:124-30
172. Mancina G, De Cesaris R, Fogari R, Lattuada S, Montemurro G, Palombo C, et al. Evaluation of the antihypertensive effect of once-a-day trandolapril by 24-hour ambulatory blood pressure. *Am J Cardiol* 1992;**70**:60D-66D
173. De Bruijn JHB, Orofiamma BA, Pauly NC. Efficacy and tolerance of trandolapril (0.5-2mg) administered for 4 weeks in patients with mild-to-moderate hypertension. *J Cardiovasc Pharmacol* 1994;**23** (Suppl 4):S60-S64
174. Messerli F, Frishman WH, Elliott WJ. Effects of verapamil and trandolapril in the treatment of hypertension. *Am J Hypertens* 1998;**11**:322-7
175. Ford NF, Fulmor IE, Nichola PS, Alpin PG, Herron JM. Fosinopril monotherapy: relationship between blood pressure reduction and time of administration. *Clin Cardiol* 1993;**16**:324-30
176. Pool JL. Antihypertensive effect of fosinopril, a new angiotensin converting enzyme inhibitor: findings of the Fosinopril Study Group II. *Clin Ther* 1990;**12**:520-33
177. Anderson RJ, Duchin KL, Gore RD, Herman TS, Michaels RS, Nichola PS, et al. Once-daily fosinopril in the treatment of hypertension. *Hypertension* 1991;**17**:636-42
178. Maclean D. Quinapril: a double-blind, placebo-controlled trial in essential hypertension. *Angiology* 1989;**40**:370-81
179. Säynävalampi P, Pörsti I, Pörsti P, Nurmi A, Seppälä E, Manninen V, et al.

- Effects of the converting enzyme inhibitor quinapril on blood pressure, renin-angiotensin system and prostanoids in essential hypertension. *J Cardiovasc Pharmacol* 1988;12:88-93
180. Gupta RK, Kjeldsen SE, Motley E, Weder AB, Sweifler AJ, Julius S. Platelet function during antihypertensive treatment with quinapril, a novel angiotensin converting enzyme inhibitor. *J Cardiovasc Pharmacol* 1991;17:13-9
181. Kjeldsen SE, Gupta RK, Krause L, Weder AB, Julius S. Does blood pressure reduction necessarily compromise cardiac function or renal hemodynamics? Effects of the angiotensin-converting enzyme inhibitor quinapril. *Am Heart J* 1992;123:1433-8
182. Black HR, Graff A, Shute D, Stoltz R, Ruff D, Levine J, et al. Valsartan, a new angiotensin II antagonist for the treatment of essential hypertension: efficacy, tolerability and safety compared to an angiotensin-converting enzyme inhibitor, lisinopril. *J Hum Hypertens* 1997;11:483-9
183. Paolisso G, Balbi V, Gambardella A, Varricchio G, Tortoriello R, Saccomanno F, et al. Lisinopril administration improves insulin action in aged patients with hypertension. *J Hum Hypertens* 1995;9:541-6
184. Thürig C, Böhlen L, Schneider M, de Courten M, Shaw SG, Riesen W, et al. Lisinopril is neutral to insulin sensitivity and serum lipoproteins in essential hypertensive patients. *Eur J Clin Pharmacol* 1995;49:21-6
185. Tomei R, Rossi L, Carbonieri E, Franceschini L, Molon G, Zardini P. Antihypertensive effect of lisinopril assessed by 24-hour ambulatory monitoring: a double-blind, placebo-controlled, cross-over study. *J Cardiovasc Pharmacol* 1992;19:911-14
186. Polónia J, Martins L, Macedo F, Faria DB, Simões, Brandão F, et al. Lisinopril and diltiazem reduce left ventricular mass without changing blood pressure in normotensive subjects with exaggerated blood pressure response to exercise. *Rev Port Cardiol* 1996;15:185-93
187. Gomez JH, Cirillo VJ, Sromovsky JA, Otterbein ES, Shaw WC, Rush JE, et al. Lisinopril dose-response relationship in essential hypertension. *Br J Clin Pharmacol* 1989;28:415-20
188. Chan P, Lin C, Tomlinson B, Lin T, Lee Y. Additive effects of diltiazem and lisinopril in treatment of elderly patients with mild-to-moderate hypertension. *Am*

J Hypertens 1997;10:743-9

189. Burris JF. The effect of ramipril on ambulatory blood pressure: a multicenter study. *J Cardiovasc Pharmacol* 1991;18 (Suppl 2):S131-3
190. McCarron D. 24-hour blood pressure profiles in hypertensive patients administered ramipril or placebo once daily: magnitude and duration of antihypertensive effects. *Clin Cardiol* 1991;14:737-42
191. Schnaper HW. Dose-response relationship of ramipril in patients with mild-to-moderate hypertension. *J Cardiovasc Pharmacol* 1991;18 (Suppl 2):S128-S130
192. Homuth V, Faulhaber H, Loose U, Löffler K, Luft FC. Usefulness of piretanide plus ramipril for systemic hypertension: a multicenter trial. *Am J Cardiol* 1993;72:666-71
193. Villamil AS, Cairns V, Witte PU, Bertolasi CA. A double-blind study to compare the efficacy, tolerance and safety of two doses of the angiotensin converting enzyme inhibitor ramipril with placebo. *Am J Cardiol* 1987;59:110D-114D
194. Guitard C, Lohmann FW, Alfiero R, Ruina M, Alvisi V. Comparison of efficacy of spirapril and enalapril in control of mild-to-moderate hypertension. *Cardiovasc Drugs Ther* 1997;11:449-57
195. Guitard C, Sassano P, Tzincoca C, Duchiez J, Safar ME. Placebo-controlled crossover comparison of spirapril at 3, 6, 12 and 24 mg once daily in mild to severe essential hypertension. *Blood Press* 1994;3 (suppl 2):61-8
196. Guitard C, Alvisi V, Maibach E, Franck J, Cocco G, Boxho G, et al. Placebo-controlled comparison of spirapril at 6, 12 and 24 mg/day in mild to severe essential hypertension. *Blood Press* 1994;3 (suppl 2):81-7
197. Fairhurst GJ. A multicentre multidose study of the efficacy and safety of spirapril in mild-to-moderate essential hypertension. *Blood Press* 1994;3 (suppl 2):77-80
198. Frishman WH, Ram CVS, McMahon FG, Chrysant SG, Graff A, Kupiec JW, et al. Comparison of amlodipine and benazepril monotherapy to amlodipine plus benazepril in patients with systemic hypertension: a randomized, double-blind, placebo-controlled, parallel-group study. *J Clin Pharmacol* 1995;35:1060-6
199. Kuschner E, Acuña E, Sevilla D, Vasquez J, Bendersky M, Resk J, et al. Treatment of patients with essential hypertension: amlodipine 5 mg/benazepril 10 mg compared with amlodipine 5 mg, benazepril 20 mg, and placebo. *Clin Ther* 1996;18:1213-24

200. Nawrocki JW, Weiss SR, Davidson MH, Sprecher DL, Schwartz SL, Lupien P-J, et al. Reduction of LDL cholesterol by 25% to 60% in patients with primary hypercholesterolemia by atorvastatin, a new HMG-CoA reductase inhibitor. *Arterioscler Thromb Vasc Biol* 1995;15:678-82
201. Wald NJ, Law MR. Serum cholesterol and ischaemic heart disease. *Atherosclerosis* 1995; 118 (Suppl): 51-5.
202. Crouse JR, Byington RP, Furberg CD. HMG-CoA reductase inhibitor therapy and stroke risk reduction: an analysis of clinical trials data. *Atherosclerosis* 1998B138:11-24
203. Boysen G, Sørensen S, Juhler M, Andersen AR, Boas J, Oslen JS, et al. Danish very-low dose aspirin after carotid endarterectomy trial. *Stroke* 1988;19:1211-15
204. Sivenius J, Cunha L, Diener H-C, Forbes C, Laakso M, Lowenthal, et al. Second European stroke prevention study: antiplatelet therapy is effective regardless of age. *Act Neurol Scand* 1999;99:54-60
205. Juul-Möller S, Edvardsson N, Jahnmatz B, Rosén A, Sørensen S, Ömblus R, et al. Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris. *Lancet* 1992;340:1421-5
206. The Salt Collaborative Group. Swedish aspirin low-dose trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischaemic events. *Lancet* 1991;338:1345-9
207. Nyman I, Larsson H, Wallentin L, and The Research Group on Instability in Coronary Artery Disease in Southeast Sweden. Prevention of serious cardiac events by low-dose aspirin in patients with silent myocardial ischaemia. *Lancet* 1992;340:497-501
208. The RISC Group. Risk of myocardial infarction and death during treatment with low dose aspirin and intravenous heparin in men with unstable coronary artery disease. *Lancet* 1990;336:827-30
209. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. *Lancet* 1989;1:175-9
210. Wallentin LC, The Research Group on Instability in Coronary Artery Disease in Southeast Sweden. Aspirin (75 mg/day) after an episode of unstable coronary artery disease: long-term effects on the risk for myocardial infarction, occurrence

- of severe angina and the need for revascularization. *J Am Coll Cardiol* 1991;18:1587-93
211. Yasue H, Ogawa H, Tanaka H, Miyazaki S, Hattori R, Saito M, et al. Effects of aspirin and *trapidil* on cardiovascular events after acute myocardial infarction. *Am J Cardiol* 1999;83:1308-13
212. Posada IS, Barriales V. Alternate-day dosing of aspirin in atrial fibrillation. *Am Heart J* 1999;138:137-43
213. Meister W, v Schacky C, Weber M, Lorenz R, Kotzur J, Reichart B, et al. Low-dose acetylsalicylic acid (100 mg/day) after aortocoronary bypass surgery: a placebo-controlled trial. *Br J Clin Pharmacol* 1984;17:703-11
214. The Medical Research Council's General Practice Research Framework. Thrombosis prevention trial: a randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. *Lancet* 1998;351:233-41
215. Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, et al. Effects of intensive blood-pressure and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 1998;351:1755-62
216. Silagy CA, McNeil JJ, Donnan GA, Tonkin AM, Worsam B, Campion K. Adverse effects of low-dose aspirin in a healthy elderly population. *Clin Pharmacol Ther* 1993;54:84-9
217. Homocysteine Lowering Trialist's Collaboration. Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomised trials. *BMJ* 1998;316:894-8
218. Wald NJ, Law M, Watt HC, Wu T, Bailey A, Johnson AM, et al. Apolipoproteins and ischaemic heart disease: implications for screening. *Lancet* 1994;343:75-9

Claims

1. A formulation comprising at least two blood pressure lowering agents, each selected from a different physiological mode of action selected from a diuretic, a beta blocker,
5 an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, and a calcium channel blocker, and an active principal from at least two of the following three categories:
 - i) at least one lipid-regulating agent,
 - ii) at least one platelet function altering agent, and
 - 10 iii) at least one serum homocysteine lowering agent.
2. A formulation according to claim 1, wherein the dose of the each blood pressure lowering agent is below the lower therapeutic dosage for the blood pressure lowering agent.
15
3. A formulation comprising active principals from at least two of the following three categories:
 - i) at least one blood pressure lowering agent,
 - ii) at least one platelet function altering agent, and
 - 20 iii) at least one serum homocysteine lowering agent,wherein the dose of the blood pressure lowering agent, if present, is below the lower therapeutic dosage for the blood pressure lowering agent.
4. A formulation comprising at least one blood pressure lowering agent and active
25 principals from at least one of the following three categories:
 - i) at least one lipid-regulating agent,
 - ii) at least one platelet function altering agent, and
 - iii) at least one serum homocysteine lowering agent,wherein the dose of the blood pressure lowering agent is below the lower therapeutic
30 dosage for the blood pressure lowering agent.
5. A formulation comprising active principals from at least three of the following four categories:

- i) at least one blood pressure lowering agent,
- ii) at least one lipid-regulating agent,
- iii) at least one platelet function altering agent, and
- iv) at least one serum homocysteine lowering agent.

5

- 6. The formulation according to any one of the preceding claims, wherein the dose of the blood pressure lowering agent is about half the lower therapeutic dosage for the blood pressure lowering agent.
- 10 7. The formulation according to any one of the preceding claims comprising:
 - i) about 12.5 mg hydrochlorothiazide, about 25 mg atenolol, and about 5 mg enalapril as blood pressure lowering agents,
 - ii) about 10 mg atorvastatin as a lipid-regulating agent,
 - iii) about 75 mg aspirin as a platelet function altering agent, and
 - 15 iv) about 0.8 mg folic acid as a serum homocysteine lowering agent; wherein each specified dose is the daily dose.
- 8. The formulation according to any one of the preceding claims comprising:
 - 20 i) about 12.5 mg hydrochlorothiazide, about 25 mg atenolol, and about 5 mg enalapril as blood pressure lowering agents,
 - ii) about 10-20 mg simvastatin as a lipid-regulating agent,
 - iii) about 75 mg aspirin as a platelet function altering agent, and
 - iv) about 0.8 mg folic acid as a serum homocysteine lowering agent; wherein each specified dose is the daily dose.
- 25 9. The formulation of any one of the preceding claims, wherein the formulation does not comprise a platelet function altering agent.
- 10. Use of active principals from two or more of the following three categories:
 - 30 i) at least one blood pressure lowering agent,
 - ii) at least one lipid-regulating agent, and
 - iii) at least one serum homocysteine lowering agent,

with or without at least one platelet function altering agent, for the manufacture of a formulation for administration to an individual without measuring, or if measured regardless of the level of, one or more of the risk factors of cardiovascular disease selected from blood pressure, serum cholesterol, serum homocysteine and platelet function.

11. Use of at least one blood pressure lowering agent and at least one active principal from at least one of the following two categories:
 - i) at least one lipid-regulating agent, and
 - 10 ii) at least one serum homocysteine lowering agent,with or without at least one platelet function altering agent, for the manufacture of a formulation for administration to an individual without measuring, or if measured regardless of the level of, one or more of the risk factors of cardiovascular disease selected from blood pressure, serum cholesterol, serum homocysteine and platelet function.
- 15 12. A method for reducing the risk of cardiovascular disease comprising administering simultaneously, separately or sequentially, active principals from at least two of the following three categories:
 - 20 i) at least one blood pressure lowering agent,
 - ii) at least one lipid-regulating agent, and
 - iii) at least one serum homocysteine lowering agent,with or without at least one platelet function altering agent, to an individual without measuring, or if measured regardless of the level of, one or more of the risk factors of cardiovascular disease selected from blood pressure, serum cholesterol, serum homocysteine and platelet function.
- 25 13. A method for reducing the risk of cardiovascular disease comprising administering simultaneously, separately or sequentially, at least one blood pressure lowering agent and at least one active principal from at least one of the following two categories:
 - 30 i) at least one lipid-regulating agent, and
 - ii) at least one serum homocysteine lowering agent,

with or without at least one platelet function altering agent, to an individual without measuring, or if measured regardless of the level of, one or more of the risk factors of cardiovascular disease selected from blood pressure, serum cholesterol, serum homocysteine and platelet function.

5

14. The use or method according to any one of claims 10 to 13, wherein the active principals are administered to an individual above a predetermined age.

15. The use or method according to any one of claims 10 to 14, wherein the method is
10 applied to an individual who has not previously been diagnosed as having had the clinical symptoms of cardiovascular disease.

16. The use or method according to any one of claims 10 to 14, wherein the method is
15 applied to an individual who has previously been diagnosed as having had the clinical symptoms of cardiovascular disease.

17. The use or method according to claim 16, wherein the cardiovascular disease is ischaemic heart disease.

20 18. The use or method according to claim 16, wherein the cardiovascular disease is stroke or transient ischaemic attack.

19. The use or method according to any one of claims 10 to 14, wherein the individual's
25 annual risk of having ischaemic heart disease or a stroke within the next 5 years is judged to be more than a specified level, statistically estimated from a combination of their age, sex and measurable risk factors such as blood pressure, serum cholesterol, serum homocysteine and smoking habits.

20. The use or method according to claim 19, wherein the specified level is 2%.
30

21. The use or method according to any one of claims 10 to 20, wherein the active principals are administered simultaneously in a single dosage form.

22. The use or method according to any one of claims 10 to 21, wherein the dosage of at least one of the active principals is selected to maximise the potency to hazard ratio, attaining a near maximal reduction of risk of cardiovascular disease whilst minimising undesirable side effects.
- 5
23. The use or method according to any one of claims 10 to 22, wherein the dose of a blood pressure lowering agent is below the lower therapeutic dosage for the blood pressure lowering agent to further maximise the potency to hazard ratio.
- 10
24. The use or method according to any one of claims 10 to 23, wherein the dose of a blood pressure lowering agent is about half the lower therapeutic dosage for the blood pressure lowering agent.
- 15
25. The use, method or formulation according to any one of the preceding claims, wherein the lipid-regulating agent is a statin.
- 20
26. The use, method or formulation according to one of the any preceding claims, wherein the platelet function altering agent is aspirin, ticlopidine, dipyridamole, clopidogrel, a glycoprotein IIb/IIIa receptor inhibitor, or a non-steroidal anti-inflammatory drug.
27. The use, method or formulation according to any one of the preceding claims, wherein the serum homocysteine lowering agent is folic acid, vitamin B6, or vitamin B12.
- 25
28. The use, method or formulation according to any one of the preceding claims, comprising:
- i) about 12.5 mg hydrochlorothiazide, about 25 mg atenolol, and about 5 mg enalapril as blood pressure lowering agents,
 - ii) about 10 mg atorvastatin as a lipid-regulating agent,
 - iii) about 75 mg aspirin as a platelet function altering agent, and
 - 30 iv) about 0.8 mg folic acid as a serum homocysteine lowering agent;
- wherein each specified dose is the daily dose.

29. The use, method or formulation according to any one of the preceding claims, comprising:

- i) about 12.5 mg hydrochlorothiazide, about 25 mg atenolol, and about 5 mg enalapril as blood pressure lowering agents,
 - 5 ii) about 10-20 mg simvastatin as a lipid-regulating agent,
 - iii) about 75 mg aspirin as a platelet function altering agent, and
 - iv) about 0.8 mg folic acid as a serum homocysteine lowering agent;
- wherein each specified dose is the daily dose.

10 30. The use, method or formulation according to any one of the preceding claims, comprising:

- i) about 12.5 mg hydrochlorothiazide, about 25 mg atenolol, and about 2.5mg amlodipine maleate as blood pressure lowering agents,
 - ii) about 10-20 mg simvastatin as lipid-regulating agent,
 - 15 iii) about 75 mg aspirin as platelet function altering agent, and
 - iv) about 0.8 mg folic acid as serum homocysteine lowering agent.
- wherein each specified dose is the daily dose.

20 31. The use, method or formulation according to any one of the preceding claims, comprising:

- i) about 12.5 mg hydrochlorothiazide, about 2.5mg amlodipine maleate, and about 5 mg enalapril as blood pressure lowering agents,
 - ii) about 10-20 mg simvastatin as lipid-regulating agent,
 - iii) about 75 mg aspirin as platelet function altering agent, and
 - 25 iv) about 0.8 mg folic acid as serum homocysteine lowering agent.
- wherein each specified dose is the daily dose.

32. The use, method or formulation according to any one of the preceding claims, further comprising an active principal from a fifth category comprising anti-oxidants.

30

33. The use, method or formulation according to any one of the preceding claims, provided in a form suitable for oral administration to a patient.

34. The use, method or formulation according to any one of the preceding claims, wherein use of the formulation reduces the risk of cardiovascular disease by at least 80%.

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FIG. 1

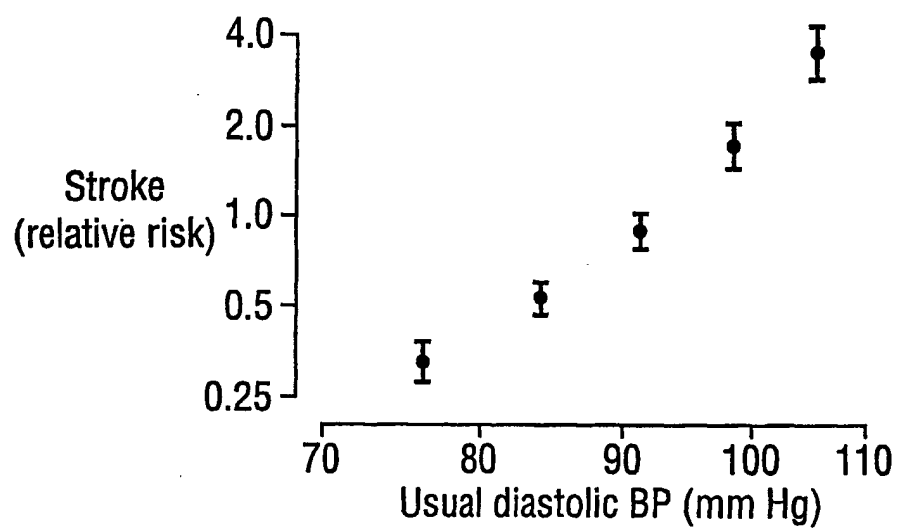
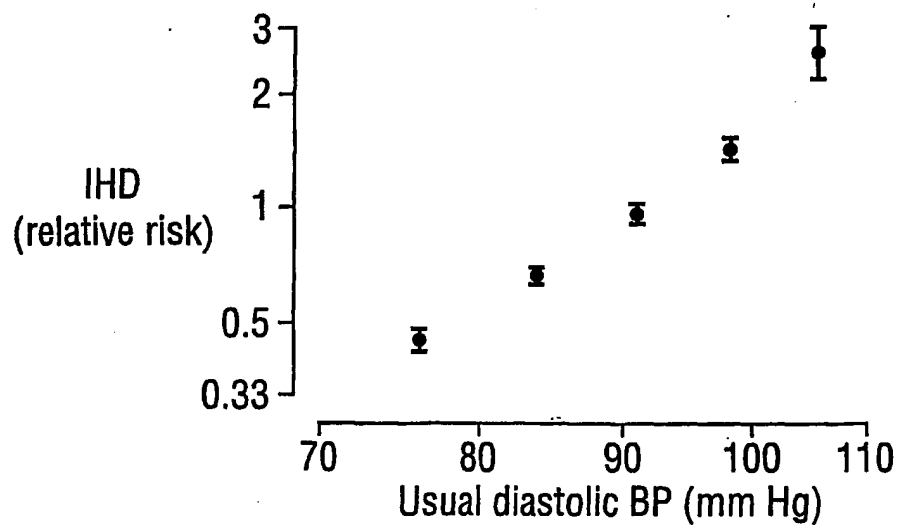


FIG. 2



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FIG. 3

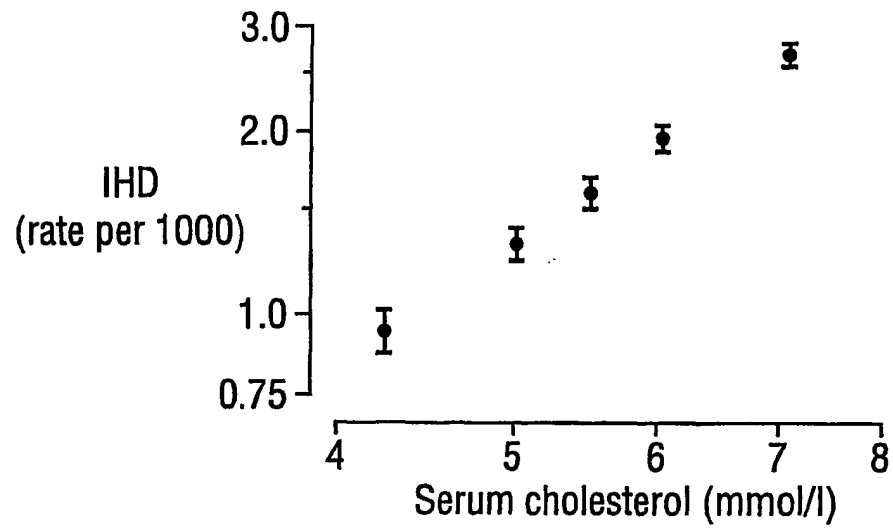
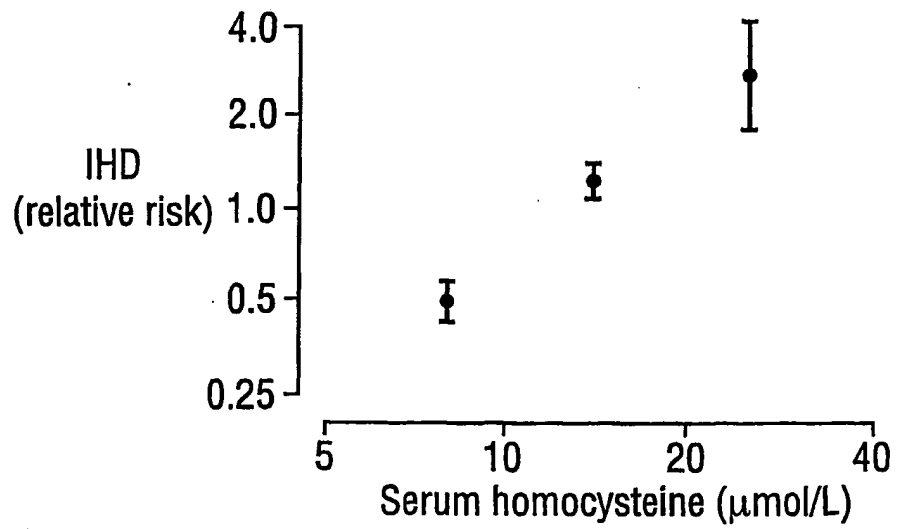


FIG. 4



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FIG. 5

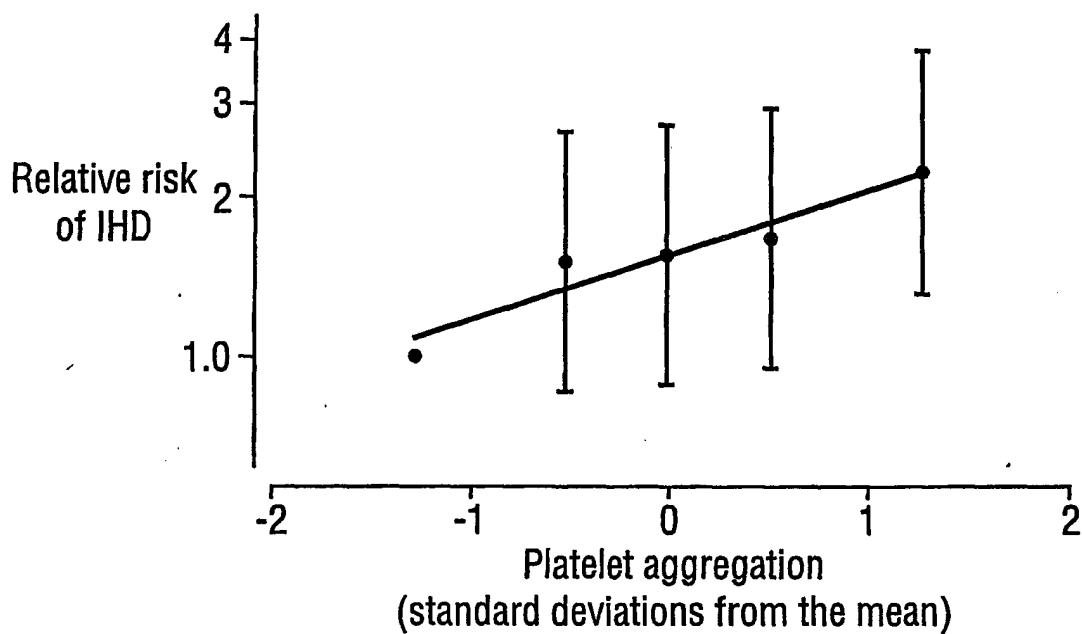
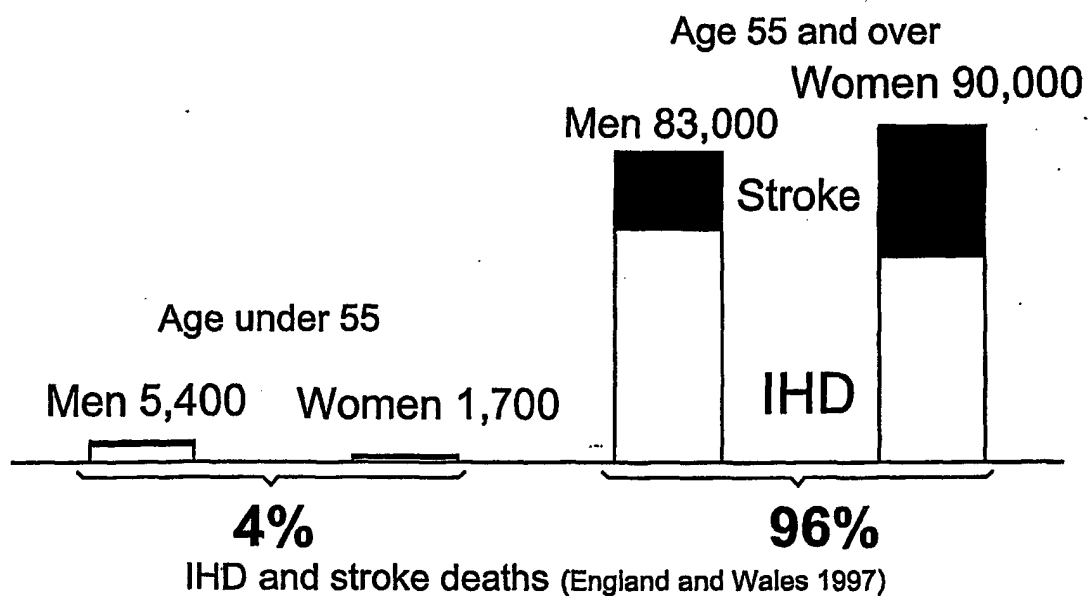
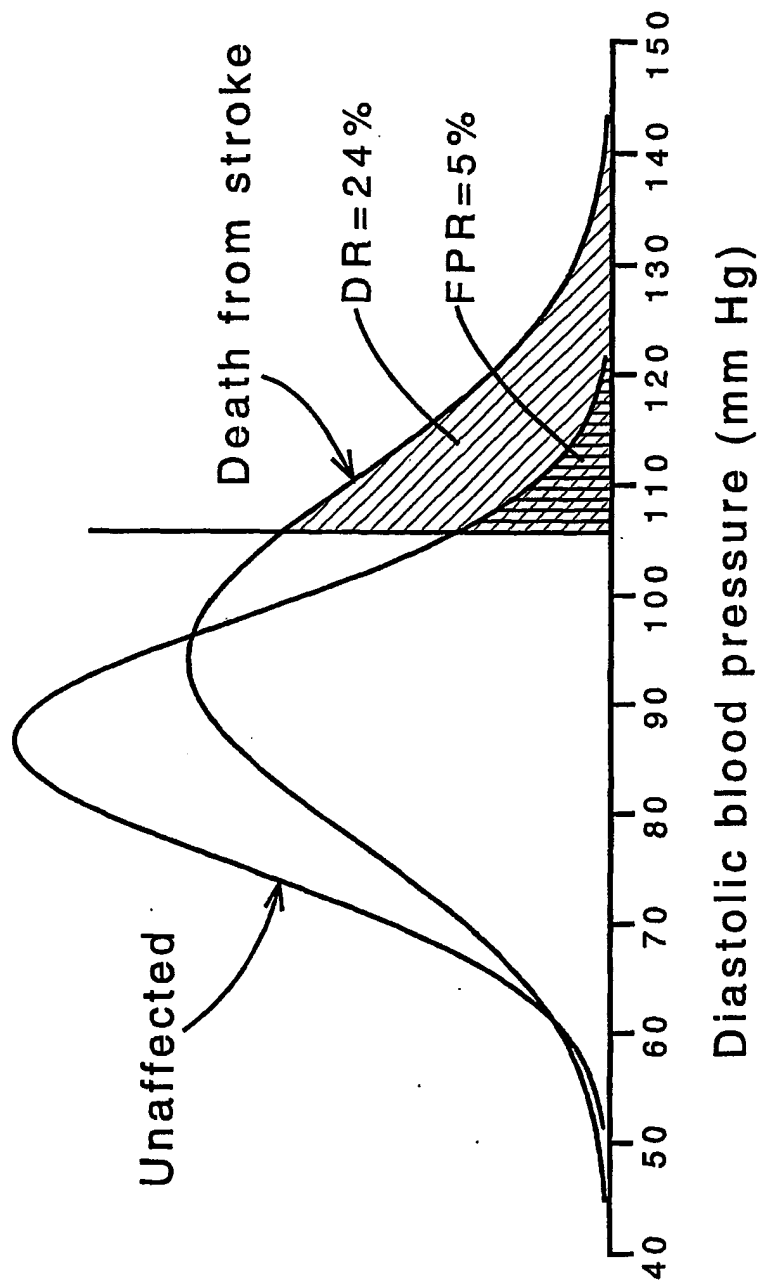


FIG. 6



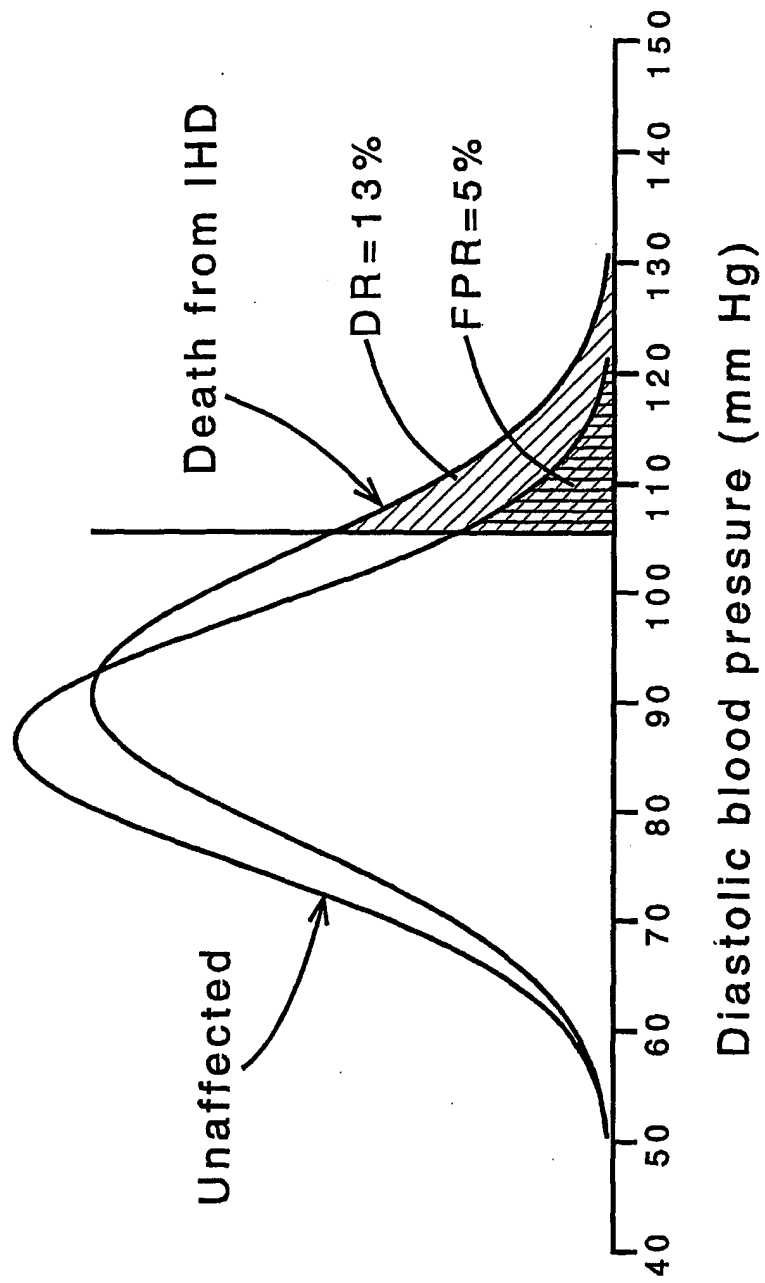
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FIG. 7



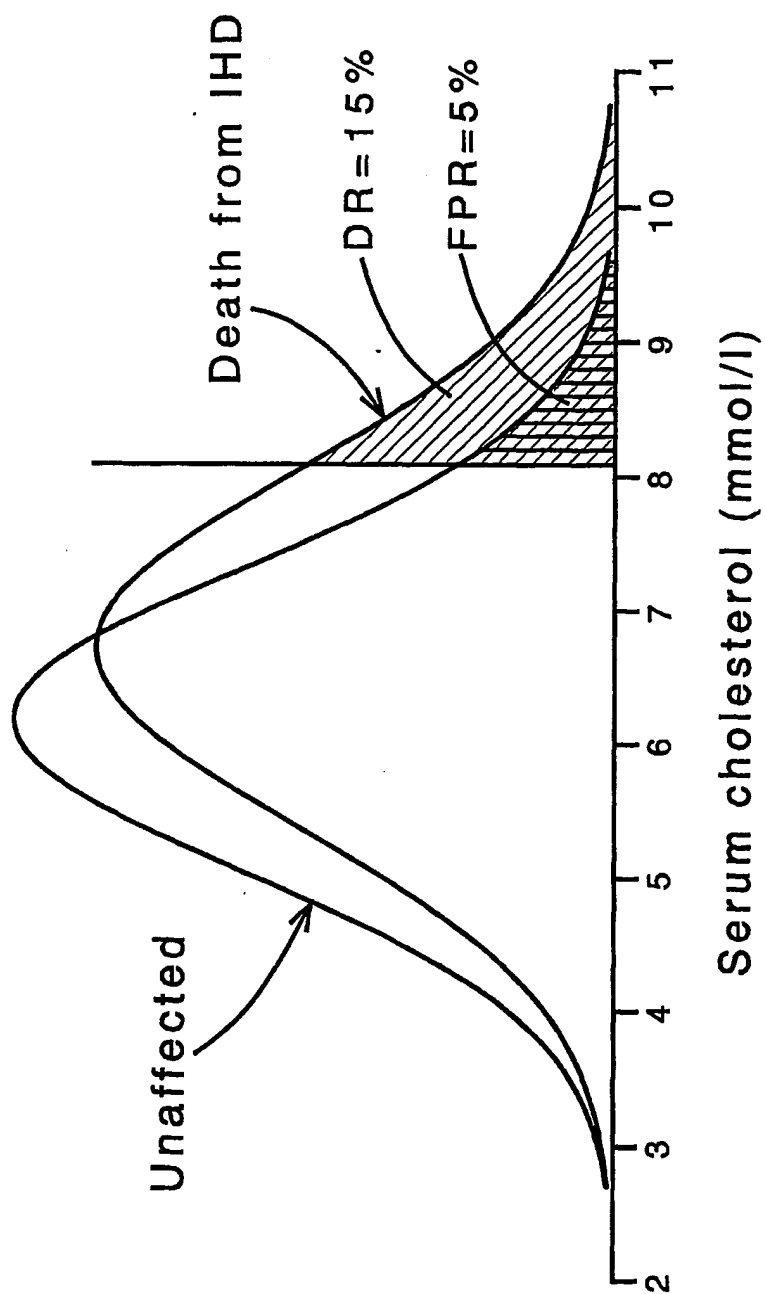
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FIG. 8



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FIG. 9



INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/GB 01/01618

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K45/06 A61P9/00 A61P9/10 A61K38/55 A61K31/54
A61K31/165 A61K31/366 A61K31/616 A61K31/519 //(A61K38/55,
31:616,31:54,31:519,31:366,31:165)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, EMBASE, MEDLINE, WPI Data, BIOSIS, CHEM ABS Data, PASCAL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 11896 A (RHYMER PATRICIA A ;OLOFSSON LARS (US); GOULD ROBERT J (US); MERCK) 26 March 1998 (1998-03-26) cited in the application page 22, line 27 -page 23, line 8; claims	3-6, 10-26, 33,34
Y	----	1-34
X	WO 98 19690 A (SQUIBB BRISTOL MYERS CO) 14 May 1998 (1998-05-14) cited in the application claims 25-28	3,4,6, 9-24,27, 33,34
X	WO 97 38694 A (TOBERT JONATHAN A ;MERCK & CO INC (US)) 23 October 1997 (1997-10-23) cited in the application claims	3-6, 9-27, 32-34
Y	----	1-34
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

31 July 2001

Date of mailing of the international search report

17/08/2001

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Seegert, K

INTERNATIONAL SEARCH REPORT

Int. onal Application No
PCT/GB 01/01618

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>NEUTEL J M: "Low - dose antihypertensive combination therapy: its rationale and role in cardiovascular risk management." AMERICAN JOURNAL OF HYPERTENSION, (1999 AUG) 12 (8 PT 2) 73S-79S. , XP000866553 abstract page 755; table 1</p>	1-34

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-6,9-27,32-34 (all partly)

Present claims 1-6,9-27,32-34 relate to an extremely large number of possible formulations. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the formulations claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the formulations, methods and uses as defined in claims 7,8,28-31 and to the general pharmacological concept underlying the present application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 01/01618

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9811896 A	26-03-1998	AU 723315 B AU 4350897 A EP 0946178 A JP 2001500875 T US 6235706 B US 6251852 B	24-08-2000 14-04-1998 06-10-1999 23-01-2001 22-05-2001 26-06-2001
WO 9819690 A	14-05-1998	AU 719290 B AU 5244298 A EP 0951293 A US 6127370 A US 6008221 A	04-05-2000 29-05-1998 27-10-1999 03-10-2000 28-12-1999
WO 9738694 A	23-10-1997	AU 732465 B AU 2666597 A CA 2251972 A EP 0904082 A JP 2000508659 T	26-04-2001 07-11-1997 23-10-1997 31-03-1999 11-07-2000